Seventeenth Annual Meeting — American College of Chest Physicians
Ambassador Hotel, Atlantic City, New Jersey, June 7-10, 1951

VOLUME XVIII NUMBER 6

DISEASES

of the

CHEST

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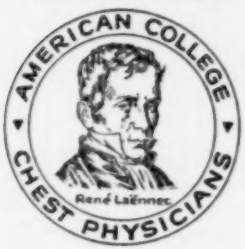

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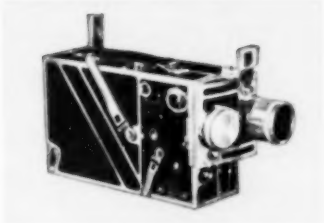

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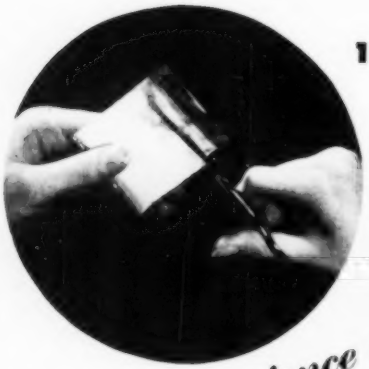

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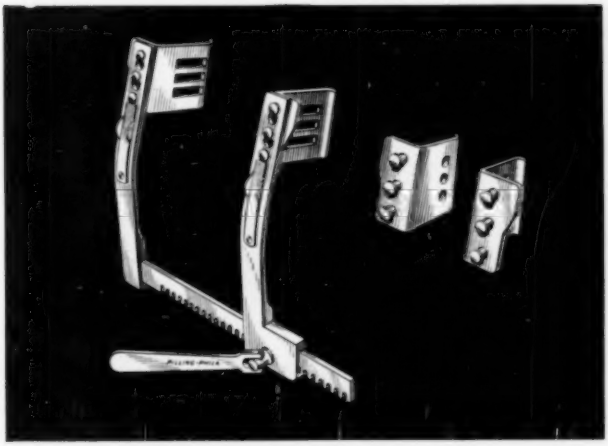

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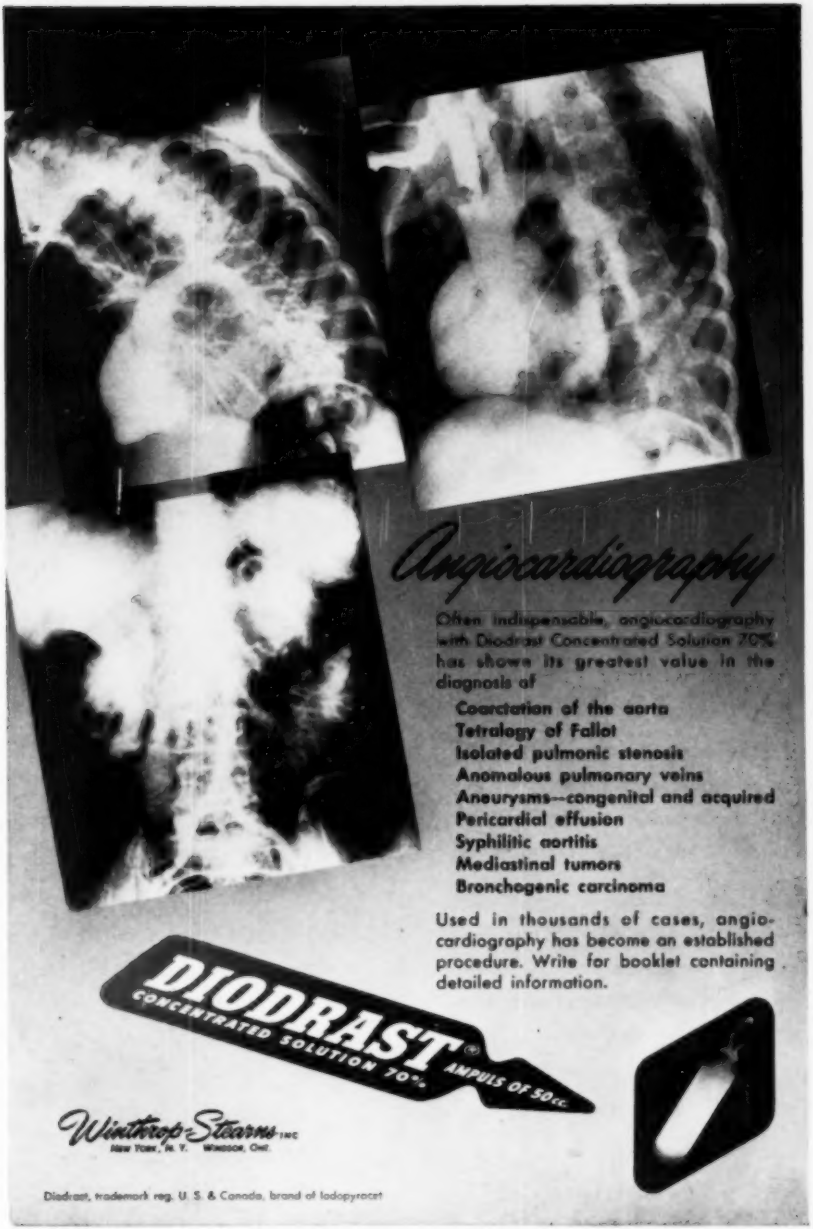
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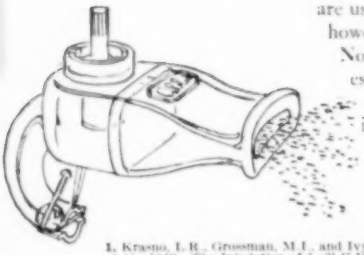

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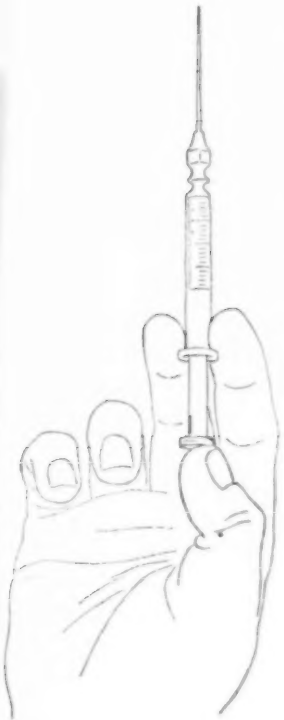

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Tibione: Laboratory and Clinical Studies*

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Tibione has been described as one of the new potent specific therapeutic agents against M. tuberculosis. This statement is based upon reports from the German literature and a single observation by competent American physicians, who feel that the drug has merit, but needs further investigation before affirming or denying its chemotherapeutic value.

The chemical is a ring compound, thiosemicarbazone which was synthesized by Behnisch and Schmidt[1] for the Bayer Company, and investigated clinically by Domagk[2] and other German workers. Among the German workers, the therapeutic indications were summarized by Mertens and Bunge.[3] Fresh pulmonary infiltrations and spreads responded best. There was evidence of healing in ulcerative lesions of the oral cavity and larynx. Improvement was noted in tuberculosis of the gastro-intestinal tract and lymph nodes. The drug was found to be ineffective in miliary tuberculosis, tuberculous meningitis, and idiopathic pleural effusion. In all of the papers which were reviewed by us from the German literature, no notation was made of toxicity, other than in a minor degree. Results of therapy were based on varying sized daily doses from 12 mgm. to 300 mgm. and in which the drug was given for varying periods of time up to nine months.

*Presented before the Los Angeles County Trudeau Society, May 23, 1950.

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In 1949, Drs. H. Corwin Hinshaw and Walsh McDermott[4] reviewed the results in 10 German institutions of two thousand patients who had received thiosemicarbazone therapy. Their recommendation, as a result of this study, was that a prompt and thorough series of experimental and clinical trials to be held in the United States. Several hospitals were designated by the Eighth Streptomycin Conference of the Veterans Administration, held in Atlanta, Georgia, in November 1949, to test the toxicity and to determine if resistance of M. tuberculosis develops to tibione.

The veterans hospitals of Birmingham and San Fernando were two of the hospitals so designated and 42 patients were treated here by the oral administration of tibione. The following report is based on therapy for 120 days.

Of the 42 patients treated, 29 had streptomycin resistant tubercle bacilli and this group received 200 mgms. of tibione daily. In the remaining 13 patients, the organisms were still sensitive to streptomycin and the patients therefore received 1 gram of streptomycin plus 200 mgms. of tibione daily. Most of the patients of this study belonged to the older age group and were selected because they had chronic disease and would be apt to have persistent positive sputum.

Method of Administration

Tibione was administered for the first week in 50 mgm. daily doses, second week 100 mgm. daily doses (50 mgm. twice daily, at breakfast and supper), and 200 mgm. from the third week on (100 mgm. twice daily, at breakfast and supper). The treatment was continued for 120 days.

Toxic Manifestations

Gastro-Intestinal Disturbances: Of the 29 patients receiving tibione alone, 10 had nausea and anorexia. Five had vomiting enough to temporarily discontinue the drug, and then went on uneventfully to finish the course.

One patient had persistent vomiting, starting with the smallest dose, 50 mgms. daily. This toxic manifestation persisted with all doses. The patient became so ill that the drug was permanently discontinued at the beginning of the fourth week.

Among the 13 patients who received streptomycin and tibione, six had nausea and anorexia. Two of these cases also had vomiting severe enough to temporarily discontinue tibione for one week. These two patients were able to return to a full dosage schedule without further gastro-intestinal disturbance.

Of the eight patients in whom vomiting occurred, this symptom developed during the third week in six, or when they were first

placed on the full 200 mgm. dose of tibione. The one mentioned above developed persistent vomiting with 50 mgms. of tibione. The eighth case developed persistent vomiting on the third week, and on restarting, could only tolerate 100 mgms.

Vertigo: Vertigo, as expected, was only present in those patients receiving combined therapy. Six of the 13 patients had severe vertigo, beginning in the third week in two, and in the seventh to the tenth weeks in the remaining four.

This vertigo was so severe and serious that it was thought advisable to discontinue permanently the streptomycin in three patients. The cold caloric test in these three patients was diminished in one, and normal in two.

The fact that so many patients in this small series had to have the streptomycin discontinued, seemingly points to an enhanced toxicity of streptomycin when used with tibione. However, the average age of this group was 48 years. It has been recognized that older persons under streptomycin therapy develop vestibular changes more rapidly and severely than younger patients.

Dermatitis: In only five patients of the entire 42 was dermatitis noted. In three, it was a mild transient macular rash which disappeared spontaneously in two to four weeks following its appearance. It caused no discomfort.

In two patients, the rash was persistent. In each case, the lesion was an exfoliative dermatitis which occurred in one on the 21st day, and in the other at the completion of his course of therapy. The drug had to be stopped in the former case. There was no concomitant eosinophilia. One patient was on combined streptomycin and tibione therapy and the other received tibione alone.

The first patient who was receiving combined therapy noted at the end of the third week a severe rapidly-spreading generalized erythematous macular rash. It appeared first over the chest and abdomen and spread rapidly over the back, arms, legs, and some to the face. This rash had somewhat the appearance of that produced by streptomycin. The streptomycin was withdrawn, but the rash continued as previously. The patient was then replaced on streptomycin and tibione was discontinued. The rash disappeared in one week, leaving only a dry, scaly skin. After two weeks, during which the patient was receiving only streptomycin, 1 gram daily, a 50 mgm. tablet of tibione was given. Within two hours a recrudescence of the erythematous macular rash occurred.

Laboratory Observations

The patients while observed had frequent blood, urine, and liver function tests at regular intervals. Among the liver function tests, the cephalin flocculation and thymol turbidity tests remained

normal throughout the course of therapy in 41 patients. One had a transitory rise in thymol turbidity to 6 units. The bromsulfalein absorption test showed abnormal findings in one instance in each of five patients. In these five patients, an icteric index was found normal at the time of the abnormal bromsulfalein absorption. Jaundice was not observed in any of the 42 persons studied.

At the Veterans Administration Hospital, Minneapolis, Minn., Dr. A. Falk[5] had eight instances where there was a bromsulfalein retention. He did liver biopsies on five of them and found fatty infiltration in the liver specimens.

In analyzing the blood changes during therapy, in 17 patients, the hemoglobin and red blood count showed a slight reduction. In all but three instances, the reduction could be explained to be within the limits of laboratory error. In the three cases mentioned, the red blood count was reduced approximately by a million red blood cells per cu. mm. There was comparable lowering of the hemoglobin in these cases. In the first mentioned, transfusions were required to counteract the severe anemia.

At the Ninth Streptomycin Conference, the Veterans Administration Hospital, Livermore, California,[6] reported that in their cases who developed anemia while being treated with tibione, they performed sternal marrow punctures. Hypoplasia of the marrow was demonstrated in these specimens.

The white blood counts remained appreciably unchanged. In one instance, the total count remained the same, but in the differential count, there was a drop in granulocytes from 67 to 37 per cent. There were two instances of transitory eosinophilia of 7 and 14 per cent.

Symptomatic Changes

Without giving leading questions, the patients were interviewed frequently. Nineteen of the 42 noted a decrease in cough. In 10, the reduction occurred in those receiving tibione alone. In nine of the 13 patients under combined therapy, a notable decrease in cough occurred. In most of them, the decrease occurred during the third week.

Sputum decrease was present in 19 of the 42 patients. The change occurred during the third week. In most of them the character of the sputum changed, becoming less purulent.

Also, of the 42 patients treated, 18 on tibione alone became concentrate negative. Besides the above consistent changes during therapy there were sporadic changes of the concentrates and cultures from positive to negative.

Changes in weight of the patients were equivocal. There were

no great changes. As many gained as lost weight. A sense of well-being was noted in six of the 14 patients on tibione therapy alone. The time of appearance was in the third week in all cases. In the combined therapy group, five noted a sense of well-being which was noted in the first and second weeks, similar to that noted with streptomycin. Two had draining fistulae-in-ano which showed clearing by the sixth week on tibione alone. One fistula cleared by the third week of combined therapy.

Analyzing the x-ray changes after 120 days of therapy, of the 29 patients receiving tibione alone, two had the treatment stopped early so that they cannot be included. Of the 27 remaining, nine improved, 16 showed no change, and two became worse. Inasmuch as these observations were on patients with chronic disease one would expect the x-ray changes to be relatively minimal. Amongst the patients receiving combined therapy seven improved, six remained unchanged, and one became worse. Reduction in the size of cavity when present, occurred in three patients, and was increased in one. The improvement with treatment was greater when combined therapy was used.

The second purpose for undertaking the problem was determining if resistance of M. tuberculosis developed towards tibione during therapy. A procedure for adequately testing the sensitivity of M. tuberculosis toward tibione was developed at Birmingham Veterans Administration Hospital, which was reported at the Ninth Streptomycin Conference and will be published. In 11 patients, whose sputum cultures remained positive throughout the course of therapy, the organisms were sensitive to tibione before therapy and resistance began to appear in the fourth week of treatment.

With regard to blood levels of tibione, the determination is made colorimetrically as described by Dr. Hendricks[7] of the Food and Drug Commission. The test gives quantitative results. The same method is used for urine determinations.

Tibione is a cumulative drug, yet it has a definite renal threshold level, as 60 to 65 per cent of all the drug is excreted unchanged in the urine in 24 hours. After three days of ingestion, three hours after the last dose while the paitent is receiving 100 mgms. daily, Dr. Hendricks found the blood level to be 2.6 mcgms. and with 200 mgms. daily it was 2.77 mcgms./ml.

Because of the comparable blood levels, at the Ninth Streptomycin Conference, a recommendation was made to reduce the daily dose of tibione to 100 mgms. This reduction of dosage may also reduce the toxicity. Further studies are now in progress to determine if the toxicity is reduced and also if 100 mgms. of tibione is therapeutically as effective as the 200 mgm. daily dose.

CONCLUSIONS

1) Tibione is a drug of moderate toxicity.

2) The greatest toxic manifestations are gastro-intestinal disturbances which develop primarily during the third week and generally persist only a short time.

3) Other complications are dermatitis, anemia, and impaired hepatic function.

4) A decrease in cough and sputum, and a sense of well-being occur with tibione.

5) Tibione is a chemotherapeutic agent capable of conversion of the sputum.

6) X-ray film improvement after 120 days of tibione therapy has been noted. The improvement is not as marked as with streptomycin for a comparable period.

7) There has been demonstrated an acquired resistance of M. tuberculosis toward tibione.

8. Tibione should be administered only where adequate laboratory facilities are available so that frequent laboratory tests can be made.

CONCLUSIONES

1) La tibiona es una droga de moderada toxicidad.

2) Las manifestaciones tóxicas más importantes son desarreglos gastro-intestinales que aparecen principalmente durante la tercera semana y que, por lo general, sólo persisten por un corto tiempo.

3) Otras complicaciones son: dermatitis, anemia y deterioro de la función hepática.

4) Disminuyen la tos y el esputo y ocurre una sensación de bienestar cuando se administra la tibiona.

5) La tibiona es un agente quimioterapéutico que es capaz de convertir el esputo.

6) Se ha observado mejoría en la película radiográfica después de 120 días de tratamiento con tibiona. Esta mejoría no es tan notable como la que causa la estreptomicina en un peréodo comparable.

7) Se ha demostrado que el M. tuberculosis adquiere resistencia a la tibiona.

8) Sólo debe administrarse la tibiona cuando existen adecuadas facilidades de laboratorio para que puedan hacerse frecuentes análisis.

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Nebulized Cortisone in Bacterial Pneumonia*

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Attention to host defense mechanisms has recently been re-emphasized. This represents a broadening of the therapeutic horizon from that of concern with the etiological factor only. In practice, however, etiological diagnosis and institution of appropriate therapy is still fundamental.

Bacteria evoke in the host a chain of reactions by which the patient attempts to defend himself. A part of the symptomatology of disease produced by bacteria is due to the effort of the host to stem the invasion. The defense mechanisms set in motion may result in a hyperreactive state which may not always be effective in combating the invader.

It has been shown experimentally that hyperreactivity of tissue to certain noxious stimuli can be markedly diminished by the administration of ACTH or Cortisone.[1] Favorable response to local Cortisone acetate (Merck) therapy of certain diseases of the eye, allergic rhinitis and nasal polypi, suggests that this steroid can manifest its effect by action at the local tissue level.[2] Pneumococcic pneumonia has responded to ACTH administered parenterally with a rapid fall of temperature and with marked subjective improvement although bacteremia and pulmonary consolidation were not affected.[3]

The purpose of this investigation was to determine whether or not Cortisone exerts its effect when applied directly to lung parenchyma and to what extent host and invader would be affected. A case believed to be suitable for trial was encountered when a patient with a sensitivity to penicillin was admitted.

A.K., No. 606964, a 60 year old white male, was admitted at 9 p.m. on April 18, 1950, to the service of Dr. B. E. Goodrich. He gave a history of developing a cough six days prior to admission. This was productive of blood-tinged, thick, yellowish sputum. There were nausea, vomiting, and right upper quadrant abdominal pain. Right chest pain was accentuated by deep inspiration and breathing was difficult for 12 hours prior to admission. System review was negative except for a long-standing stasis dermatitis of the lower extremities, moderate deafness, and a history of penicillin sensitivity. There had been no previous respiratory illness. He had received no therapy prior to admission.

The patient appeared toxic, dehydrated, cyanotic, and had an expiratory grunt. The temperature was 104.6 degrees F., pulse 100 per minute,

*From the Henry Ford Hospital, Detroit, Michigan.

respirations 28 per minute, blood pressure 120/60. The skin was warm and dry. Eye, ear, nose and throat examination was negative except the teeth were in poor repair, tongue was red and dry, and the throat moderately hyperemic. No adenopathy was noted. Abnormal physical findings were confined to the chest. They consisted of dullness to percussion over the upper two-thirds of the right chest anteriorly and posteriorly, increased tactile fremitus, whispered pectoriloquy, and tubular breath sounds. At the right apex posteriorly egophony was present. Sticky rales were heard at both bases.

Examination of the heart including an electrocardiogram was normal. The abdomen was soft. There was tenderness at the right costal margin, but the liver was not palpable. The lower extremities showed moderate varicosities and stasis dermatitis. Rectal and neurological examinations were normal.

Total WBC count was 18,400, predominately polymorphonuclear leukocytes. Blood carbon dioxide combining power was 37.4 per cent, diastase 44 per cent, sugar 94 mgm. per cent, and NPN 32 mgm. per cent. Urinalysis was not unusual except for a 1 plus albumin and occasional RBC and WBC. Sputum was easily raised and appeared rusty-gray in color. Microscopic examination showed polymorphonuclear leucocytes and pneumococci (Type VII by the Quellung technique). Blood cultured revealed Type VII pneumococci.

Roentgenographic examination of the chest showed dense infiltration involving the upper right lung compatible with a diagnosis of lobar pneumonia.

Twenty-five mgm. of Cortone (Merck) (11 dehydro-17 hydroxycortico steroid acetate) was diluted with 4 cc. normal saline and 1 cc. of this mixture was given by the aerosol technique every 30 minutes. Thus the patient received 5 mgm. of Cortisone acetate by inhalation every half

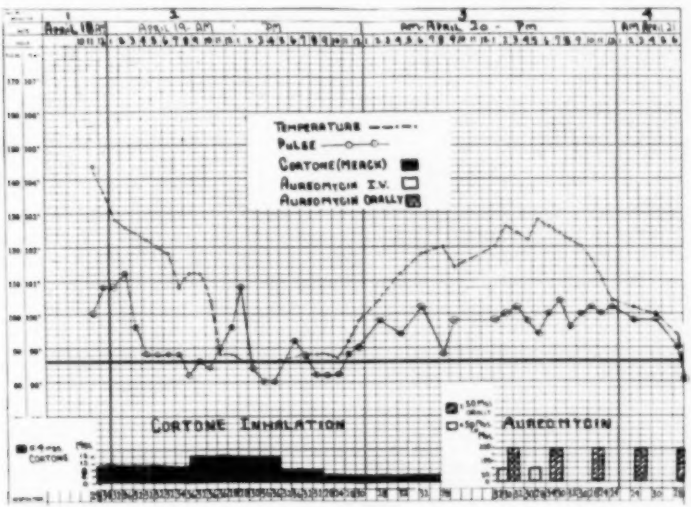

CHART I

PRE-TREATMENT
4 HRS. OF CUTTROSE
(Pneumo still alive)
11 HRS. OF CUTTROSE
A
B
C

hour beginning at 11 p. m. on April 18, 1950. No other therapy was given during the period of Cortisone treatment, except intravenous fluids to maintain hydration.

A progressive fall in temperature occurred throughout the night (see Chart I). After 12 hours and with profuse diaphoresis, the temperature reached a normal level. Subjectively the patient felt more alert. He appeared less toxic and less dyspneic, showed no cyanosis, and was greatly relieved of pain three hours after the initiation of therapy. Five hours later, he desired food for the first time in four days. The feeling of well-being was not accompanied by any marked clearing of the lungs by x-ray. X-ray films were taken at four, seven, 17, and 33 hour periods (see films).

The white count at the eight hour period had fallen to 8,800 with 95 per cent polys (see Chart II). A blood culture taken 12 hours after the initiation of therapy was still positive for Type VII pneumococci. Cultures from this point on were negative.

The eosinophile counts did not show any striking changes, ranging between 0 and 13 during Cortisone therapy (done by the direct technique according to Thorn and Forsham). After eight hours of therapy the concentration of Cortisone was increased to 8 mgm. per cc. every 30 minutes. Approximately 18 hours after starting therapy, inhalations were given every hour, 8 mgm. per cc. The second reduction in dose to 5 mgm. per cc. every hour was begun after 22 hours. Two hours after the second dose reduction the temperature which for the preceding 12 hours had been normal, rose progressively and reached 102 degrees F.

The drug was discontinued after 33 hours due to exhaustion of the supply. During the next six hours no therapy was administered. During this period all the signs of toxicity, cyanosis, dyspnea and accentuation of the right upper quadrant pain occurred. In addition, a transient mental depression occurred.

At the conclusion of Cortisone inhalation the patient began to raise considerable blood-tinged sputum. It was the impression of the examiners that there had been definite improvement of the chest findings. The egophony and splinting of the chest had disappeared. Breath tones had a more vesicular quality and the percussion note was less impaired. This was poorly shown by x-ray films over the period of Cortisone adminis-

CHART II

Pneumococcal Pneumonia Treated by Cortisone Inhalation

Hospital Days:	1	— 2 —		— 3 —		— 4 —		— 5 —	
	PM	AM	PM	AM	PM	AM	PM	AM	PM
Blood Culture									
Leucocytes Per CU. MM.	+	0	+	0	—	0	—	—	0
Total X 1000	18.40	8.80	10.95	15.50	13.75	7.15	—	9.95	—
P.M.N. X 1000	16.56	8.36	9.96	13.95	13.33	6.72	—	8.96	—
Lymphs X 1000	1.84	.44	.88	1.55	.28	.43	—	.99	—
Monos X 1000	0	0	.11	0 †	.14	0	—	0	—

†Cortisone Discontinued

TERMINATION OF CORTISONE
313 MGM.---33 HOURS
30 HRS. AFTER TERMINATION
OF CORTISONE
DISCHARGE STATUS

D E F

tration. A total of 313.0 mgm. of Cortisone was administered by the inhalation technique over a period of 33 hours.

Six hours after withdrawal of Cortisone 100 mgm. of aureomycin was given intravenously and the dose was repeated after three hours. Subsequent doses of 250 mgm. of aureomycin were given orally at four-hour intervals. No other antibiotics were used. The temperature began to fall progressively five hours after the administration of aureomycin and reached normal in 14 hours. Ten hours after aureomycin was begun, the patient felt and appeared less toxic, but the pain and cough continued. Over the next three days his cough and chest pain decreased and the temperature continued to fall toward a normal level. X-ray and physical findings over the ensuing days showed a slow but progressive clearing of the pneumonia. There was a transient friction rub at the right base posteriorly for a 24-hour period detected on the second day of aureomycin therapy. This disappeared concurrently with an increase in the pleural effusion. The effusion was of small magnitude and steadily decreased. Bronchoscopy four days after the administration of Cortisone revealed only the usual post-pneumonic mucosa.

Aureomycin therapy was terminated after nine days. The patient continued to feel well and was discharged on the 14th hospital day with minimal residual chest findings and x-ray evidence of resolving pneumonia.

Discussion

The capillary bed of the lungs is enormous when compared with that of other organs. Whether or not absorption of Cortisone occurred at this level and to what degree is unknown. There was no satisfactory measurement available. The mode of action could have been systemic or it could have occurred at the site of application in the lung parenchyma. Eosinophile counts, initially low, were inconclusive as a measure of the amount of effective Cortisone administered. It is our belief that the rapid subjective improvement and fall of temperature shown was due to Cortisone. It should be emphasized that the disease process in the lungs was apparently not affected.

We found no report of the use of Cortisone by inhalation. These observations are unique in demonstarting that Cortisone applied directly to the lungs by inhalation in a patient with inflammatory pulmonary disease is effective in causing rapid remission of symptoms. However, these observations do not justify a statement of the efficacy of the agent in the general treatment of pneumonia. It is possible that accessibility of bacteria to antibiotics may be facilitated by the use of Cortisone. Certain exudative processes in the eye and the infiltrate of pulmonary tuberculosis have resolved when Cortisone was administered.[4,5]

Nebulized Cortisone appears to be as effective as that administered parenterally. Inhalations of Cortisone in the dilutions used do not appear to be irritating to trachea or bronchi.

SUMMARY AND CONCLUSIONS

A patient with Type VII pneumococcic pneumonia who was given Cortisone by inhalation is presented.

1) Cortisone inhalation appears to be as effective as parenteral administration.
2) The reaction of the host to the disease was favorably influenced.
3) The bacterial agent was not influenced.
4) Additional comfort and security may be afforded the critically ill patient by the use of Cortisone.

Addendum: Other cases of pneumonia are being similarly treated and will be reported at a later date.

Acknowledgment: The Cortisone used was obtained from Dr. J. M. Carlisle of Merck and Company through the courtesy of the Opthalmology Research Group of the Henry Ford Hospital.[4] Dr. R. R. Margulis assisted in the management of this case.

RESUMEN Y CONCLUSIONES

Se presenta un paciente con neumonía neumocóccica, causada por el Tipo VII, que recibió inhalaciones de Cortisona.

1) La inhalación de la Cortisona parece ser tan eficaz como la administración parenteral.
2) Se influyó favorablemente la reacción del huésped a la enfermedad.
3) No se influyó el factor bacteriano.
4) Mediante el uso de la Cortisona se le pueden proporcionar solaz y seguridad adicionales a los enfermos graves.

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A Water-Soluble Contrast Medium for Bronchography

Report on Clinical Use†

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The ideal material for bronchography should be:

(1) non-irritating to the lungs and productive of no general reaction,
(2) miscible with bronchial secretions,
(3) quickly and easily eliminated from the lungs,
(4) capable of filling or outlining even the smaller bronchi without filling the alveoli,
(5) capable of maintaining the filling until x-ray films can be exposed,
(6) capable of giving good contrast roentgenogram,
(7) easy to administer,
(8) capable of giving consistently diagnostic x-ray films.

Unfortunately, no material has been found which fulfills all of these requirements. Any substance which enters the lungs must act as a foreign body. For example, even normal saline probably produces a mild reaction in the lungs.[1]

Iodized oils have for many years been unchallenged as a medium for the x-ray diagnosis of diseases of the bronchi. These oils have certain inherent properties which offer serious objections, the chief of these being their slow resorption with the consequent addition of retained radiopaque densities to confuse the x-ray picture for long periods.[2,3] This is due to the fact that oils are insoluble in bronchial secretions and that the iodine is slowly liberated from the oil. In addition to this slow resorption, iodized oils offer further objections: radiopacity is fixed by the constant iodine content, viscosity is fixed by the chemical nature of the oil, oil causes a marked macrophagic reaction of long duration,[2,3] lipoid pneumonia and granuloma have been reported[4] and since iodine is slowly liberated from the oil,[5] iodism occasionally occurs.

In 1948, Morales and Heiwinkel[6] reported on the use of a water-

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soluble contrast medium, Viscous Umbradil. This mixture consists essentially of Iodopyracet* (diethanolamine salt of 3,5 - diiodo - 4 - pyridone - N - acetic acid) and sodium carboxymethylcellulose (CMC).[R] Morales[7] and Fischer[8] have subsequently demonstrated its usefulness.

In addition to being water-soluble, the viscosity can be varied within wide limits and yet the surface tension is low enough to allow the material to reach the smallest bronchi. By varying the viscosity, any degree of filling can be obtained. The low viscosity medium produces a thin covering of the mucosa while the higher viscosity material fills only the large bronchi. The medium of extremely low viscosity, however, frequently causes marked alveolar filling with obliteration of detail in the bronchi. All traces of this radiopaque material disappear from the lungs by x-ray in three to five hours since the material is easily coughed up and the Iodopyracet is quickly absorbed.

Fate in the Body

The fate of the constituents of this medium in the body has been studied by various workers. Umbradil (brand of iodopyracet) and other similar organic iodide compounds are rapidly absorbed and excreted by the kidneys. This is well established by the use of these compounds in arteriography and urography.[9]

The fate of the CMC[R] is more complicated. Being water-soluble, much of this material is eliminated by the normal cleansing mechanism of the lung and by postural drainage. Brown and Houghton,[10] and Werle[11] gave CMC[R] to animals and man by mouth and were unable to demonstrate any evidence of absorption or deleterious effects. Shelanski[12] extended these studies and used CMC[R] as a vehicle for medications. Thus, this material is now used as a thickener for ice cream, as a vehicle for medication, and as an antacid in the treatment of peptic ulcer.

Hueper,[13] using dogs, gave CMC[R] intravenously each day for a period of three months. Small amounts were found in the reticuloendothelial system of the liver and spleen, in the endothelium of the renal glomeruli, and in the renal tubules. It was found to much less degree than acacia or other gum preparations. They concluded from their investigation that CMC[R] was probably excreted by the kidney and was not harmful.

Hellstrom and Holmgren[1] injected large amounts of Visous Umbradil, Umbradil, CMC,[R] and saline into the lungs of rats and rabbits. They noted a transient thickening of the alveolar septum most marked with Umbradil, less so with Viscous Umbradil and

*Iodopyracet is marketed in this country as Diodrast[R] (Winthrop-Stearns).

CMC[R] in that order. There was a macrophagic response with all materials including saline. In the case of Viscous Umbradil this reaction, which is quite similar to that seen with iodized oil, had completely subsided within three weeks. Further, the trachea showed no changes.

To be certain of our own supply of CMC,[R]* one cc. of a 2 per cent solution was injected into the peritoneal cavity of small white mice on five consecutive days. None of the animals died. All were sacrificed on the sixth day and no gross abnormalities could be found. Microscopically, small amorphous deposits could be seen on the peritoneal surfaces, but there was practically no cellular response.

The Medium

Viscous Umbradil B,** as supplied, consists of Umbradil 50 per cent, sodium carboyxmethylcellulose (CMC[R]) 2.6 per cent, and a local anesthetic, Xylocaine (diethylaminoaceto-2,6-xylidide), 0.5 per cent. With this material we had difficulty in preventing alveolar filling. The content of CMC[R] was therefore increased to 3.3 per cent, using high viscosity, food grade type CMC.[R] In our hands this has given consistently better results and has markedly decreased the amount of alveolar filling, thus keeping the material from the area where the main reaction occurs in the lungs.[1] The viscosity can, however, be varied to suit the needs of the user.

Technique of Injection

The patients are prepared by giving nembutal 0.1 gm. one hour, and codeine 60 mgm., atropine 0.4 mgm. one half hour before the procedure. Pontocaine[R] 1 per cent is used to anesthetize the larynx, pharynx, and vocal cords. A small rubber catheter is then introduced through the nose and into the upper trachea. The trachea and bronchi are then anesthetized by instilling Pontocaine[R] 1 per cent through the catheter and positioning the patient to insure thorough, wide-spread anesthesia. This is essential. Five to 10 minutes should be allowed for the anesthesia to take full effect since Viscous Umbradil is a little more likely to produce coughing than are oils. A total of about 6 cc. of 1 per cent Pontocaine[R] has been adequate and has produced no reactions. Symptoms of Pontocaine reaction should be watched for, however, and intravenous barbiturate should always be immediately available.

The Viscous Umbradil mixture is then injected slowly through the catheter and the patient is positioned to secure filling of the

*The CMC[R] for this investigation was supplied through the courtesy of Hercules Powder Co., Wilmington, Delaware.

**The Viscous Umbradil B was supplied through the courtesy of Astra Pharmaceutical Products, Inc., Worcester, Massachusetts.

bronchi of one lung. This may be followed fluoroscopically. Speed and efficiency after injection and filling is important since there is a tendency for the material in the upper lobe to flow into the lower. Upright stereoscopic posterior-anterior and appropriate oblique x-ray films are then made. The opposite lung may then be examined in a like manner. About 10 to 15 cc. of Viscous Umbradil are needed for each lung. The fact that the Viscous Umbradil contains 0.5 per cent of a local anesthetic must be taken into account in considering the total anesthetic used.

X-ray Technique

The technique of taking films varies slightly from that used with iodized oil. Viscous Umbradil has slightly less contrast than do oils but this is easily compensated for by the x-ray technique. Morales[7] recommends exposure as for "normal chest x-rays." Our films have been made at a tube-to-film distance of 66 inches and about 5 KV has been added to the exposures for normal chest films in the various positions. With this technique the contrast is entirely satisfactory. Stereoscopic viewing adds to the diagnostic value of the films.

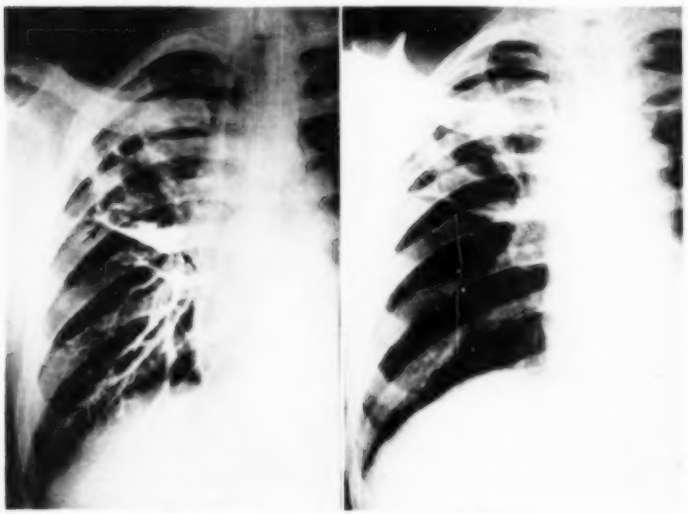

FIGURE 1a FIGURE 1b

Figure 1a, Case 1: Abscess of right upper lobe. Bronchogram showing large defect in upper lobe (arrows) and upward displacement of right middle lobe bronchus.—*Figure 1b, Case 1:* Roentgenogram taken five hours after bronchography without postural drainage. Artifact over shoulder.

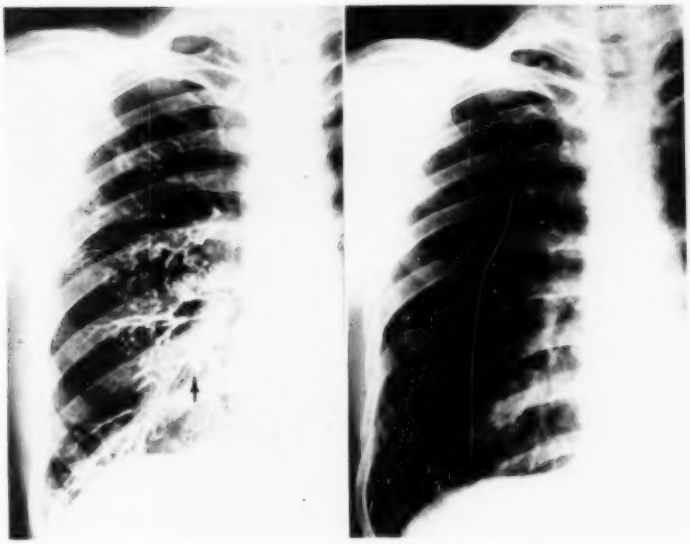

FIGURE 2a FIGURE 2b

Figure 2a, Case 2: Bronchogram. The posterior basic segment is obstructed (arrow).—*Fig. 2b, Case 2:* Roentgenogram five hours following bronchography.

FIGURE 3a FIGURE 3b

Figure 3a, Case 3: Complete collapse of right upper lobe (arrows). There is rotation and displacement of the right middle lobe bronchus.—*Figure 3b, Case 3:* Roentgenogram five hours following bronchography.

Discussion

The various bronchograms presented in this paper were made with the material and technique as presented. Postural drainage following bronchography was purposely omitted. The subsequent x-ray films were made about five hours after completion of the procedure. Some of our earlier films which were made using a less viscous medium showed rather marked alveolar filling. Even in these instances, x-ray films made five hours later were entirely clear. It is obvious that there is no residual to confuse the x-ray picture later. Furthermore, the procedure with Viscous Umbradil can be repeated the next day if too much alveolar filling is apparent on the first attempt at bronchography. This "second attempt" is often impossible with iodized oils because of retained radiopaque material.

Three of our patients had transient, mild elevation of temperature 12 to 24 hours following bronchography. One of these had been bronchoscoped immediately prior and had had a similar elevation following routine bronchoscopy 10 days before. The second patient was having rather marked pleuritic pain at the time of bronchography but no other evidence of acute infection was noted. In the third instance, bronchiectasis was apparently quiescent. On subsequent roentgenograms there was no evidence of any change in the pre-existing pathology. In our experience, temperature elevation is also seen not infrequently following the injection of iodized oils.

To date we have seen no reaction to iodine. Because of the stability and rapidity of excretion of Umbradil, further experience may show that this material can be used even where a history of iodine sensitivity exists.

The contraindications to the use of Viscous Umbradil are: (1) the presence of acute respiratory infection, (2) sensitivity to Umbradil (rare), and (3) acute nephritis or uremia since Umbradil is excreted by the kidney.

Viscous Umbradil contains 0.5 per cent of xylocaine, a local anesthetic. In our technique we have been well aware of the fact that two anesthetic agents have been used. This should probably be eliminated.

CONCLUSION

In our experience Viscous Umbradil, a viscous, water-soluble, radiopaque medium, has many advantages over iodized oil in bronchography. We feel that the advantages far out-weigh the disadvantages. Bronchograms with this medium are diagnostic and there is complete absorption of the radiopaque material in three

to five hours without any clinically demonstrable deleterious effect on the lungs. Certainly Viscous Umbradil deserves extensive trial and further evaluation.

Acknowledgment: We are indebted to Dr. George Baylin, Dr. E. A. Stead, Jr., and Dr. E. E. Menefee, Jr., for their advice in this investigation and to Mr. John Cahoon for his help in developing an x-ray technique.

CONCLUSION

En nuestra experiencia el *Umbradil Viscoso*, un medio viscoso, soluble en agua y radio opaco, tiene muchas ventajas sobre el aceite yodado en la broncografía. Opinamos que sus ventajas más que sobrepasan sus desventajas. Los broncogramas obtenidos con este medio son diagnósticos y se absorbe completamente la substancia radio opaca en tres o cinco horas, sin ningún efecto nocivo al pulmón. El *Umbradil Viscoso* merece un ensayo general para que se determine su valor en la broncografía.

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The Prognostic Significance of Idiopathic Pleural Effusion*

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The practicing physician, despite mass chest x-ray surveys and similar programs, must still remain the most important single factor in tuberculosis case finding. Early case finding and treatment are the major tenets of effective tuberculosis control, as they are in any communicable disease, and have been practiced most diligently in many areas. The presence of parenchymal pulmonary lesions by x-ray, symptomatology and bacteriologic study of the sputum or gastric expressions are frequently in themselves diagnostic of tuberculosis or prompt continued study and observation of the patient to evaluate the presumptive diagnosis. Unfortunately, however, the role of the so-called "idiopathic" pleural effusion as one of the important early manifestations of tuberculous infection is less readily recognized by many physicians and the opportunity for control of the tuberculous process in its minimal phase is not infrequently lost. The lack of positive diagnostic etiologic findings, either laboratory or x-ray, has undoubtedly in most instances contributed to this difficulty. It is the purpose of this paper to emphasize the basic importance of this entity as a clinical manifestation of active tuberculous infection and the necessity for early treatment to avoid its known and varied complications.

Pleural effusions occur as complications in many diseases, chiefly the bacterial or viral pneumonitides, rheumatic fever, invasion of the pleura by neoplastic tissue or lymphoma, congestive heart failure, renal disease and tuberculosis. The differential diagnosis of the underlying disease in these instances and the characteristics of complicating pleural effusion have been described extensively in standard textbooks and the literature, and need not be elaborated here. The age of the patient, symptoms, bacteriologic studies, response to drug or antibiotic therapy will frequently substantiate or narrow the clinical impressions within a short time. It is the

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group whose clinical course and findings suggest a tuberculous etiology, but in whom it cannot be proven, that are usually relegated to the "idiopathic" category. It is this group that requires the most careful consideration by the physician and has the highest incidence of subsequent tuberculous manifestations.

The incidence of patients with idiopathic pleural effusion reaches its peak at about age 20, and the majority are age 30 or under (Fig. 1). The distribution indicates that it is usually found in late adolescence and early adulthood, and comparison with the curve for the age distribution of pulmonary tuberculosis indicates a very significant dissimilarity. A recent study of 1365 cases by Eberle[1] notes a peak incidence at the age of 16 in males and a wider distribution at age 17 to 22 in females. Males predominate in the adolescent and adult groups, but not in children. Its major incidence in this important economic and social age group further stresses the need for its clinical recognition as a tuberculous process.

Adequate studies of the racial incidence of primary pleural effusion are not available, although it is generally accepted that Negroes have a higher incidence of tuberculous disease and a less favorable course and prognosis than the white race. Kraft[2] found a 14 per cent incidence among Negroes in a series of 100 cases of primary pleural effusion in Army personnel, and Karron and Purves[3] an incidence of 22 per cent among non-whites (chiefly Negroes) in a similar series of 215 cases at an Army Tuberculosis Center. Jones and Dooley[4] in a study primarily of Negro patients consider tuberculous pleurisy with effusion a more frequent manifestation of widespread extrapulmonary disease than among white patients, with a much higher (16 per cent) mortality. More fre-

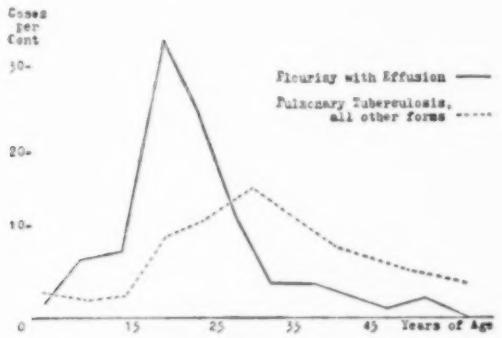

FIGURE 1 (From Thompson, B. C., *Am. Rev. Tuberc.*, 54:349, 1946): Age distribution of 190 patients with pleurisy with effusion compared with that of 2,540 cases of pulmonary tuberculosis.

quent and widespread pulmonary disease, as well as extrapulmonary dissemination, secondary to primary pleural effusion in the Negro is reported, with earlier appearance, poorer prognosis and higher mortality of these complications following the inadequately treated initial manifestations.

The frequency of pleural effusion as a manifestation of tuberculosis in the age group cited has been considered by many investigators to be a reaction subsequent to the development of tuberculin sensitivity during a primary tuberculous infection. The increase of these effusions in England during the war years, as well as in our own military forces, has been attributed to the entry of young male adults who have escaped their first tuberculous infection in childhood into industrial or military life where they may be exposed to sudden massive doses of tubercle bacilli. Similar transitions resulting from population movements from protected tuberculin negative environments to those less well controlled, such as leaving for schooling or employment in larger cities and towns, may also contribute to a continued incidence. The mechanism is apparently different from that in childhood tuberculosis, where pleural effusion as a manifestation of primary infection is infrequent.

Edwards[5] observed a group of nurses on whom monthly tuberculin skin tests were applied and found that there was an average interval of six months between the development of skin allergy to tuberculin and the onset of pleurisy with effusion. Arborelius[6] found that one-third of a group of Swedish army conscripts with initially negative Mantoux reactions developed pleurisy with effusion within a six-month period of the Mantoux reaction becoming positive. Similarly, Israel and Long[7] reported that primary tuberculous infection in adults, as evidenced by a change in tuberculin sensitivity from negative to positive, may be followed after a short interval by an attack of pleurisy, without other manifest intrathoracic tuberculosis. Malmros and Hedvall[8] in a careful investigation of nearly 3000 students and student nurses found that parenchymal tuberculosis appeared at an average of 10 months after the first positive Mantoux, with frequent interpolation of a pleural effusion. These findings have been confirmed by many other investigators and indicate that pleurisy with effusion in the majority of instances is a manifestation of a post-primary tuberculous infection.

The pathogenesis and mechanism for the production of idiopathic or post-primary effusion is perhaps best explained on the basis of the work of both Patterson[9] and Rich,[10] who found that the injection of viable tubercle bacilli into the pleural space or other serous cavities of a normal test animal produced little or

no local reaction and no fluid. The similar introduction of tubercle bacilli into an animal previously infected with tubercle bacilli and consequently in a hyperallergic or hypersensitive state would result in considerable pleural reaction with the exudation of serum, leukocytes, red cells and fibrin to produce a characteristic effusion. A similar reaction might also occur from the introduction of dead tubercle bacilli or the protein portions of destroyed bacilli, as might result from the evacuation of a caseous focus, but only in a previously sensitized animal.

The production of tuberculous pleural effusion in man is believed to follow a somewhat similar train of events. The generally accepted mechanism is that of an extension to the pleura of tubercle bacilli from a primary subpleural focus in an individual who has become sensitized as a result of the primary infection. Erwin[11] has also postulated that a caseous primary tracheobronchial node may penetrate into the sensitized pleura with production of an inflammatory exudate. This may be a more likely mechanism in children in whom tuberculous hilar adenopathy is frequent, but is probably an infrequent occurrence in the older age groups. Pinner[12] states that even if no parenchymal lesions are demonstrable, the presence of a pleural or subpleural tuberculous focus as the source of pleural infection should be postulated. Hematogenous dissemination is probably a rare source for the production of tuberculous effusion, particularly when unilateral, but may be implicated in the infrequent, simultaneous bilateral pleural effusion. Pleural effusion may be the first evidence of hematogenous or parenchymal miliary tuberculosis, may occur subsequent to the extension of re-infection parenchymal tuberculosis or at any stage of pulmonary tuberculosis, but such effusions differ materially in mechanism, course and prognosis from those of the post-primary infection or "idiopathic" variety.

The signs and symptoms of post-primary pleural effusion are variable in their onset, severity, findings and duration. Physical signs vary with the amount of fluid in the pleural space or fibrin deposition on the pleural surfaces. Rigler[13] has noted that as much as 400 cc. of fluid may be present in the pleural space and not demonstrable by the usual posterio-anterior chest film, but lateral decubitus films may be quite helpful in revealing small amounts of fluid.

Laboratory studies in pleural effusion have been extensive, but with the exception of positive bacteriologic results do not contribute reliable criteria for diagnosis. Pinner and Moerke[14] after an extensive study concluded that neither chemical nor cytological nor serologic data per se offered dependable diagnostic or prognostic criteria. The various clinical tests and studies will not be

detailed here, except for some comment upon their clinical significance.

The tuberculin skin test is almost invariably positive in primary pleural effusion, usually to a fresh preparation of first strength PPD or 1:1000 Old Tuberculin. A small number of cases may require second strength doses to produce a significant reaction in the absence of an adequate response to the lower dilutions. The absence of a positive skin test should cast considerable doubt upon the tuberculous etiology of the effusion. The possibility of an effusion following so rapidly after the primary infection that tuberculin allergy has not developed and the skin test is negative cannot be excluded, but is unlikely. Should the skin test remain negative for a period of six to eight weeks following the appearance of the effusion, the possible tuberculous etiology of the effusion can nearly always be discarded. The tuberculin skin test, particularly if the previous reaction of the patient is known to have been recently negative, may contribute considerably toward the etiologic evaluation of the effusion in the absence of definitive bacteriologic studies.

The erythrocyte sedimentation rate is usually increased and falls to normal values with the subsidence of the clinical signs and the effusion. Not uncommonly the sedimentation rate remains moderately elevated for a considerable period after the effusion has subsided due to the residual fibrinous process or the activity of some other tuberculous focus which is not evident. It is most important that the early return of the sedimentation rate to normal values should not be considered an evidence of complete subsidence of the tuberculous process and an indication to allow the patient to resume activity. It is a not uncommon experience in the treatment of active pulmonary tuberculosis to find that the sedimentation rate falls to a normal range while the patient is on bed rest, even though the lesions remain unchanged and other evidences of an active process are apparent. The active tuberculous process which precipitated the effusion must be overcome by the normal defense mechanisms of the body and this requires a much longer period of convalescence than may be reflected by the fall in sedimentation rate. The sedimentation rate may serve as a guide to the duration of the acute phase or of continuing activity, but clinical reliance upon it directed toward adequate treatment of the patient must be limited.

Every effort should be made to obtain pleural fluid, particularly for bacteriologic study. Culture and guinea pig inoculation of the fluid for the demonstration of tubercle bacilli should be done in every instance. Direct smears of the fluid are of little value, since tubercle bacilli are rarely numerous in such effusions. Positive

bacteriologic results by both culture and animal inoculation are reported in only 20 to 35 per cent in various series, but guinea pig inoculation has given positive results more frequently than culture. Success in obtaining positive bacteriologic results from pleural fluid will depend on the frequency with which fluid is aspirated and bacteriologically studied. The highest percentage of positive results has been obtained by those investigators who secure at least 500 cc. of fluid for concentration prior to culture and are able to secure consecutive specimens for such study.

Although only about 35 per cent positive bacteriologic results on pleural fluid are reported by the most careful investigators, a negative report should not be considered as evidence that the fluid is not the result of a tuberculous process. Reports of filterable or atypical tubercle bacilli which do not grow with the usual laboratory techniques, the possibility in some cases that the pleural process is based on an antigen-antibody reaction without viable bacilli[9,10] or the paucity of bacilli in the fluid at the time the specimen is taken may offer some explanation for the failure to demonstrate the organism bacteriologically in all cases. Kraft's[2] data indicates that 14 of 21 cases who developed pulmonary tuberculosis within one year from the onset of primary pleural effusion had bacteriologically negative pleural fluids, even though very adequate studies were made. The results in other well studied series reinforce the value of positive bacteriologic findings, but decry the fallacy of accepting negative findings as critical evidence of non-tuberculous etiology.

The pleural fluid sugar content has recently been suggested as a diagnostic aid in the determination of the tuberculous etiology of pleural effusion by Gelenger and Wiggers.[15] Values below 30 mgs. per 100 cc. were considered diagnostic of a tuberculous etiology, based on cases with fluid later proved to be tuberculous. Values between 30 and 60 mgs. per 100 cc. were considered presumptive evidence and those above 60 mgs. per 100 cc. as non-tuberculous in origin. These findings are interesting, but the small size of their series makes further evaluation necessary.

The treatment of patients with pleural effusion may be divided into two categories, that of the acute period with the problem of the effusion and that following the acute period directed toward control of the underlying process. Any course of treatment must have as its basis the recognition of these effusions as a manifestation of frank, active and early tuberculosis. Kraft[2] stresses that the responsibility upon the physician to regard these effusions as "probably tuberculous" and to initiate recognized treatment is tremendous. Landau[16] neatly summarizes her viewpoint by stating, "It is more logical to speak of investigations in

the prognosis of a recent primary infection, indicated by the appearance of an idiopathic pleural effusion than place pleural effusion and its prognosis into a special category."

The acute phase of the illness with its fever, chest pain and development of fluid is best treated symptomatically. The pain usually subsides rapidly as fluid forms. The problem of the removal of accumulated fluid in the pleural space has been the basis for several approaches depending chiefly upon the frequency of aspiration and quantity withdrawn. The removal of only a small amount of fluid for diagnostic purposes in the early phase of the process, delaying the removal of the larger portion until the acute phase has subsided or the fluid has spontaneously absorbed, unless pressure symptoms supervene to make aspiration mandatory, has been the usually suggested method. However, the fibrin content in the pleural fluid is known to be usually high and even a slight delay in the adequate removal of a considerable effusion may result in extensive deposition of fibrin, with formation of fibrinothorax and often severe and permanent compression of the lung. Feldman and Lewis[17] adopted an eight-week period of observation in their series, during which the effusion was given an opportunity to absorb, with aspiration following if fluid persisted. They noted that even with this relatively short delay in the evacuation of fluid, chronic thickening of the pleural membranes and spontaneous coagulation of the whole exudate had taken place in many instances with marked impairment of pulmonary function.

Anticoagulants such as sodium citrate and heparin have been injected into the pleural space to prevent coagulation of the fluid and deposition of fibrin, but without notable effect. Recent studies[18] suggest that a fibrinolytic agent, such as streptokinase, may prove to be of benefit in preventing fibrin deposition in the pleural space or removing deposits recently formed. The injection of air into the pleural space to prevent adherence of the pleural layers has also been recommended, but it is extremely doubtful that this measure has ever preserved the integrity of the pleural space. A small pneumothorax of 200 cc. of air may be very helpful in visualizing the underlying lung for evidence of parenchymal involvement, but according to Amberson[19] should otherwise be avoided, as it interferes with healing and prolongs the exudation of fluid.

The approach to the control of the effusion itself at this hospital has been primarily to secure fluid for diagnostic purposes, even when the effusion is very small. With larger effusions every effort is made to keep the pleural space as dry as possible, although strenuous efforts are not made to secure fluid accumula-

tions remaining below the level of the dome of the diaphragm. It is felt that 500 to 1000 cc. of fluid can usually be safely removed at one sitting and aspirations repeated at daily intervals if necessary, until the desired result is obtained. Removal of fluid allows the underlying lung to be adequately visualized roentgenographically, retards the deposition of fibrin upon the pleura and adds considerably to the comfort of the patient. "Pocketing" of fluid may occur, sometimes very early in the process, but careful fluoroscopic observation or the use of roentgenograms taken in lateral and oblique views frequently localizes the area sufficiently to allow adequate aspiration.

We have been considerably impressed with the residual damage to lung ventilatory function that may occur secondarily to the deposition of fibrin from pleural effusion, usually from failure to aspirate the pleural space frequently and adequately when fibrin formation is rapid. Although considerable resolution of such deposits may take place over a period of years, the finding of obliteration of the costophrenic angle, impaired motion of the diaphragm, mediastinal fixation or a "bound" lung with narrowing of the rib interspaces and pulmonary crippling after pleural effusion are not infrequent residuals. Such impairment may be of considerable importance to the patient's future welfare and physical ability, as well as the possible control of tuberculosis or other pulmonary disease that may subsequently develop in either lung. Two cases illustrating this problem are cited below.

J. O., a 25 year old white male student, was admitted on March 9, 1949. He had been a patient at a private hospital from November 1947 to early January 1948 for treatment of left pleurisy with effusion initially diagnosed as pneumonia (Fig. 2). One thousand cc. of fluid was removed on each of two aspirations, but bacteriologic studies were not done. Tuberculin skin test was reported positive at that time. At discharge he was told that his chest "was not entirely clear," but was advised to rest at home for three months and then return to school, which he did. The patient admits that though he remained indoors most of the time, he was in bed very little. He did not again consult his physician until after a chest survey film taken in November 1948 was reported suspicious of parenchymal disease, but had remained entirely asymptomatic during the intervening period.

Admission chest film revealed extensive pleural reaction on the left, with a cavity in the right mid-lung field (Fig. 2). Sputum concentrates and cultures were positive for acid-fast bacilli. Bronchoscopy on April 12, 1949 revealed a normal tracheo-bronchial tree. It was realized that any need for collapse therapy on the right would depend on function of the left lung. Bronchospirometric studies revealed pulmonary function on the left to be approximately one-third that on the right, with vital capacity determinations of 300 cc. and 2000 cc. respectively. Excellent patient cooperation was secured on a strict bed rest program with fortunate gradual clearing of the cavity and conversion of sputum and gastric

cultures to negative. Planigrams taken in December 1949 failed to reveal any evidence of residual cavitation in the right lung.

Comment: This patient had about six weeks of hospitalization and was discharged to his home with an active pleural process. The patient was not told of the implications of his illness, nor was any planned period of observation indicated. Subsequent organization of the fibrinothorax re-

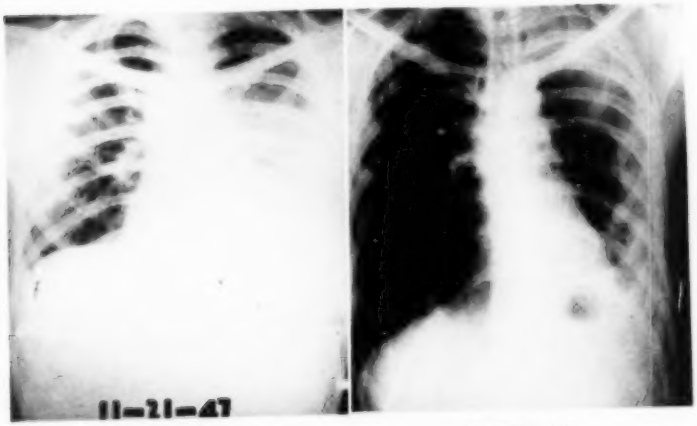

FIGURE 2a FIGURE 2b

Figure 2a, Case J.O.: Film taken November 21, 1947 at onset of pleural effusion, which later involved entire left pleural space.—*Figure 2b:* Film taken March 10, 1949 demonstrating marked residual pleural reaction on left 16 months later, with tuberculous cavity in hilar area of the right lung.

FIGURE 3a FIGURE 3b

Figure 3a, Case N.H.: Admission film taken June 12, 1948 showing extensive left pleural effusion with heart displaced to the right, and normal right lung. *Figure 3b:* Film taken March 29, 1949 reveals parenchymal disease in left lower lobe and large tuberculous cavity in left midlung field. The pleural reaction on the left has entirely subsided.

sulted in marked impairment of pulmonary ventilatory function, which might have seriously impeded treatment of the lesion in the contralateral lung had it not responded to bed rest alone. Active pulmonary tuberculosis was demonstrable within one year from the onset of the pleurisy with effusion. The problem of the severely impaired left lung function remains and decortication of the pleura may be considered in the future to improve ventilatory function.

D. H., a 19 year old white male soldier, was admitted on July 14, 1949. On June 28, 1949 while home on furlough he had noted right chest aching, fever, malaise and several drenching night sweats. Treatment with sulfadiazine and penicillin at home did not ameliorate his symptoms and he was transferred to this hospital. In May 1949 he had had an illness lasting several days, with fever, nausea and vomiting and vague chest tightness and aching but this subsided rapidly and no studies were made. Upon admission he was acutely ill, and chest films revealed fluid or pleural reaction at both lung bases, most marked on the left (Fig. 5). Fluid was obtained on several aspirations from the left pleural space, but aspiration attempts were repeatedly unsuccessful on the right. The aspirated fluid was positive for tubercle bacilli on culture. Bone marrow aspiration revealed no tubercles or granulomata suggesting hematogenous tuberculous dissemination. Tuberclin skin test was positive. Fever gradually subsided to normal over a period of four months, but sedimentation rate remained moderately elevated. Repeated sputa and gastric aspirations were bacteriologically negative.

Chest films revealed no evidence of parenchymal disease, but extensive pleural thickening was present bilaterally, most marked on the right. Bronchospirometric studies revealed pulmonary function on the right to be approximately 50 per cent of that on the left.

Comment: It is likely that the process on the right antedated that on the left, rather than this being a simultaneous bilateral effusion. Considerable impairment of pulmonary function already exists and pleural decortication may be indicated in the future to improve function.

The use of antibiotics such as penicillin and aureomycin during the acute phase of a primary pleural effusion appears to have little or no effect, as might be expected from the etiology of such effusions. Such agents are not infrequently used during the acute period before the diagnosis becomes obvious, but their continued use is not beneficial or warranted unless specific indications exist. The intrapleural instillation of penicillin is similarly of no value and by some observers has been implicated in the production of increased effusion and increased fibrin deposition, particularly when dosage above 25,000 units is employed. The use of such dosage intrapleurally may be indicated when very frequent aspirations are necessary and a break in sterile technique is feared.

The advent of streptomycin in the treatment of tuberculosis has suggested its use in the treatment of pleural effusion, of either suspected or proved tuberculous bacteriologic identity. The danger of the emergence of streptomycin-resistant tubercle bacilli which might well preclude retreatment in a future critical need

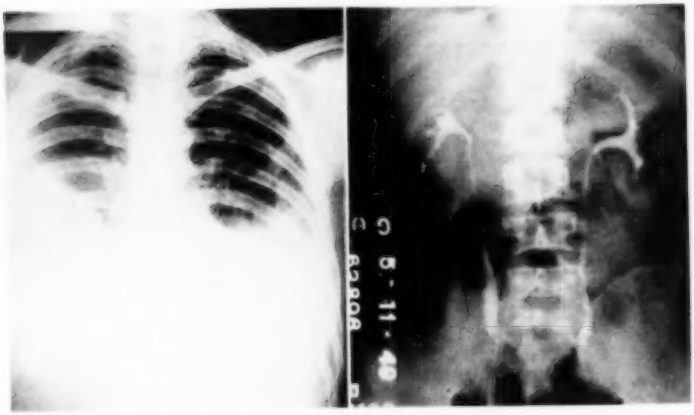

FIGURE 4a FIGURE 4b

Figure 4a, Case I.S.: Army film taken February 28, 1945 reveals bilateral pleural effusion four months after onset.—*Figure 4b*: Film taken May 11, 1949 reveals destruction of superior pole, major calyx, of right kidney due to tuberculosis.

FIGURE 5. Case D.H.: Admission film taken July 14, 1949 reveals bilateral pleural effusion, most marked on the right. Little change on the right had occurred to February 1950, and pulmonary function is markedly impaired on that side (see text).

has been a valid argument against the treatment of primary pleural effusion as well as minimal pulmonary tuberculosis, both of which usually respond well to conservative therapy. The introduction of PAS (para-amino salicylic acid), which appears to have a delaying effect on the emergence of resistance to streptomycin when given in combined dosage, as well as a primary therapeutic effect when used alone, may offer an agent of value in the treatment of patients with extensive bilateral effusions, a maintained acute phase with recurrent effusion, continued fever and toxicity, or other evidences of an unfavorable course. Moyer[20] has recently reported a small series showing very favorable response to such therapy, when the usual therapeutic regimen had not been effective. Other anti-tuberculosis drugs are now in experimental use or on the horizon which may offer effective therapy in all forms of tuberculosis, without fear of toxicity or the emergence of resistant strains of tubercle bacilli. The use of streptomycin intrapleurally in primary pleural effusion is without value, and its use in the treatment of post-primary pleural effusion should be strictly reserved for those few instances cited where there is unfavorable response to the usual regimen. Those who have had extensive experience with this antibiotic and realize its limitations and dangers advise strongly against its indiscriminate use in the treatment of tuberculous disease.

Other than the treatment of the acute phase and the effusion itself, the primary concern of the physician should be with the therapeutic implications of the underlying process. The primary or idiopathic pleural effusion is not infrequently followed by tuberculosis of the reinfection type, pulmonary or extrapulmonary in location. It is estimated that about 15 per cent of cases of pulmonary tuberculosis have had a previous pleurisy with effusion. Pulmonary lesions may be present concomitantly with the effusion but hidden by it or the pleural reaction, or may appear soon after the effusion and clinical signs subside. If the patient is prematurely discharged or lost to observation at this point, the implications are obvious. It is against these frequently insidious manifestations of tuberculosis following the effusion, that the most careful vigilance should be employed. The pleural effusion may be small or subside rapidly, but the very fact of its presence affords the physician a clinical signal of invaluable significance. Landau[16] states that the effusion is at any age only a symptom without prognostic importance, but the presence of an active underlying focus is axiomatic and this focus is likely to follow its course steadily, consistently and sometimes inexorably. The problem of pleural effusion was recognized early in the war and resulted in the issuance of a War Department Technical Bulletin

(TB Med. 71) in July 1944 emphasizing the probable tuberculous origin of any "idiopathic" effusion in young adults and the need for adequate diagnosis and treatment.

Numerous reports in the literature have indicated that the incidence of pulmonary tuberculosis following idiopathic pleural effusion varies from 17 to 50 per cent, but is considered to be 25 to 35 per cent in the United States. The results of some of the larger surveys are shown in Table I. Although based on a five-year observation period, an analysis of the reports indicates that the greatest incidence usually occurred within the first year following the pleural effusion. Kraft[2] in a carefully followed series of 100 cases of primary pleural effusion in Army personnel found that 21 per cent developed pulmonary tuberculosis within one year, averaging 6.2 months, and all while on a sanatorium regimen. Thompson[21] reports a "breakdown" rate in the first year following the primary effusion of more than 50 per cent of the five year total. The incidence of subsequent extrapulmonary tuberculosis is about 15 per cent, is not infrequently found in association with pulmonary involvement and usually affects the genito-urinary tract, bone, peritoneum or lymph nodes. The mortality rate from subsequent tuberculosis during the five year observation period is estimated at about 10 per cent, although this varies considerably with nationality, race, extent of disease and treatment. Table I indicates the variance in mortality statistics from reported series. The extremely high rate of 71 per cent in Farber's series reflects a group which had no sanatorium care following the acute phase of the effusion. Jones and Dooley[4] reported a mortality

TABLE I

Incidence of Pulmonary Tuberculosis Following Idiopathic Pleural Effusion

Author	Year	No. Cases	Pulm. Tuberc. No.	Pulm. Tuberc. Pct.	Observation Years	Deaths Per Cent
Gaarde[24]	1930	126	50	40	1-26	
Schuman[25]	1941	94	38	40	5	
Bonilla[23]	1942	40	9	23	5	
Farber[*26]	1943	111	38	34	5	71
Jones and Dooley[4]	1946	99	16	16	2	20
			23	12	1	
Thompson[21]	1946	190	47	25	5	3.5
Kraft[2]	1949	100	21	21	1	0

*None had sanatorium care following the acute phase.

rate of 20 per cent in their series, mainly Negroes with extensive extrapulmonary dissemination. Thompson's[21] series, reflecting better initial care, had a five year mortality rate of only 3.5 per cent. Bonilla[23] found a 9 per cent mortality in a five year follow-up of patients who had four months of bed rest after onset of pleurisy with effusion, but a 24 per cent mortality in the group refusing such care. The influence of adequate care and treatment upon subsequent tuberculous dissemination and mortality rate cannot be underestimated.

All authors agree upon the necessity for adequate sanatorium care or very carefully supervised bed rest at home, if favorable conditions for such home treatment exist, for patients convalescing from pleurisy with effusion. Lowry[22] states that 7 to 13 per cent of those cases of pleural effusion who receive at least four to six months of sanatorium care at the time of their effusion will later develop pulmonary tuberculosis, compared to a morbidity of 30 to 50 per cent in those not receiving adequate care. Amberson[19] similarly recommends convalescence under sanatorium conditions of four to six months, while Kraft[2] recommends at least one year of good sanatorium care. One cannot overstress the importance of the first year following the effusion when sanatorium care may not only prevent complications but allow detection of subsequent lesions when effective therapeutic measures can be applied and further dissemination controlled. Bonilla[23] found that patients whose lesions became known during rest had a better prognosis than those whose lesions, after the effusion, were first detected during periods of physical activity. Several cases noting these aspects of treatment and complications are cited below.

J. G., a 23 year old white male student, was admitted on January 27, 1949, with history of cough, fever, left chest pain and weight loss of one month's duration. He had been previously hospitalized here from August 1946 to February 1947 for treatment of left pleurisy with effusion, from which aspirated fluid was bacteriologically negative. Tuberculin skin test was positive. He was rehospitalized within three weeks for treatment of right pleurisy with effusion, also bacteriologically negative, and was again discharged in October 1947. He was seen once subsequently for a follow-up examination, but apparently ignored further invitations to return. He began attending radio school in the Spring of 1948, and in September 1948 began working an additional six to eight hours daily in a radio repair shop. Symptoms began in December 1948 leading to his readmission.

Findings on admission revealed fibro-cavernous disease in the left upper lung field, residuals of the previous pleural effusions and positive direct smears of the sputum for tubercle bacilli. Previous chest films had shown no parenchymal disease. Despite bed rest and streptomycin the lesions did not respond, positive sputum continued and left thoracoplasty

was done in October 1949. There has been no evidence of extra-pulmonary involvement. Bronchospirometry studies prior to thoracoplasty revealed a ventilatory equivalent of 2.6 on the right, compared to 1.2 on the left, indicating impairment of pulmonary function from pleural residuals on the right.

Comment: This patient had two episodes of pleurisy with effusion with six and eight months of hospitalization respectively for each episode. Lack of cooperation on the part of the patient and failure of adequate observation resulted in the appearance of extensive parenchymal disease within 26 months of the initial effusion.

N. H., a 23 year old white male carpenter was admitted on June 12, 1948. In February 1948 while employed on Guam he noted pleuritic pain in the left chest, malaise and fever. His chest was strapped by a physician, and he returned to work, with subsidence of all symptoms in a few days. In late May 1948, while in San Francisco, he again had pain in the left chest, malaise, fever and a 10 pound weight loss and was found to have pleural effusion. Tuberculin skin test was positive at that time. Immediate hospitalization was recommended, but he returned to Minnesota. Upon admission he was found to have considerable fluid in the left chest and about 2500 cc. was removed on several aspirations, but was negative on culture. Several sputum smears were positive shortly after admission. Chest films (Fig. 3) indicated a parenchymal cavitary lesion in the left lower lung field and a left phrenemphraxis was done in July 1948 with almost immediate sputum conversion. The patient remained on bed rest and did very well until March 1949 when positive sputa were again reported and chest films revealed a cavity in the left lower lobe. He was given a course of streptomycin and pneumoperitoneum instituted but without favorable effect upon the cavity or sputum findings. A left lower lobectomy was done in July 1949 with a subsequent uneventful course and negative sputum and gastric bacteriologic findings.

Comment: Parenchymal disease with positive sputum evidently existed at the time of the second episode of pleurisy with effusion, yet the aspirated fluid was bacteriologically negative. This again demonstrates the false sense of security that may come from placing definitive reliance upon negative findings in this entity.

I. S., a 29 year old white male student was admitted on February 17, 1949. A right pleurisy with effusion was noted in October 1944, while in the Army, with subsequent involvement on the left. A positive guinea pig was reported from right pleural fluid. He was kept at "bed rest" in various Army hospitals and in March 1945 a small infiltration was noted in the apex of the right lung which stabilized rapidly and without the finding of positive sputum or gastric studies. He was discharged in the Fall of 1945.

He was seen from time to time at another Veterans Administration hospital and remained well until January 1947, when a left apical lesion was noted as well as some reaccumulation of fluid at the right base. He received bed rest and sanatorium care until July 1948, when he left against medical advice. Bacteriologic studies of the sputum were negative, as were those of small amounts of fluid aspirated from a pleural "pocket" on the right. The apical lesion did not increase and stabilized satisfactorily. He was again followed at another Veterans Administration

hospital and remained apparently well, although small amounts of fluid were aspirated from time to time from the right pleural pocket which were positive on culture for tubercle bacilli. He was transferred to this hospital for possible surgical treatment of the pleural pocket. Frequent aspirations secured small amounts of serous fluid, which remained positive for tubercle bacilli, and eventually resulted in apparent cessation of fluid formation and obliteration of the pocket.

Shortly after admission the patient was found to have an increase in white blood cells, a few red blood cells and a trace of albumin in the urine on repeated specimens. Cultures of bladder urine were positive for tubercle bacilli. Intravenous pyelography (Fig. 4), retrograde studies and bacteriologic studies of ureteral urine specimens revealed destruction of the superior pole of the major calyx of the right kidney, with urine specimens from that kidney alone positive for tubercle bacilli. Right nephrectomy was done on August 9, 1949 with an adjunct course of streptomycin. Histologic study revealed an active tuberculous cavity in the upper pole of the kidney. Repeated urine cultures since nephrectomy have been negative. Sputum and gastric cultures are negative, as is a bone survey of the entire spine.

Comment: Despite a year of presumed inactivity following the initial right pleural effusion, the patient developed an apical infiltrate within six months and subsequently a similar infiltrate on the contralateral side, reactivation of the pleural effusion and eventually renal tuberculosis. This man is a very intelligent individual to whom the significance of his initial pleural effusion was never adequately explained, with consequent tendency to circumvent adequate bed rest while in the Army. This case illustrates the need for careful indoctrination of the patient, adequate primary care and for continued observation of these cases for a considerable period following their first illness.

G. M., a 26 year old white male farmer was admitted on July 21, 1949. He had had left chest pain in March 1948, diagnosed as "pleurisy" on the basis of an x-ray film taken by his physician at that time. He remained at home for a few days and then resumed his usual activities. In May 1948 a small mass was noted on the anterior chest, overlying the sixth costo-sternal junction. This was curetted and reported as "ill defined granuloma" histologically. A draining sinus persisted at the site subsequently. In November 1948 stiffness and swelling of the left knee was noted, gradually increasing to involve the leg almost to the ankle. Aspiration of the knee joint at another Veterans Administration hospital in April 1949 secured purulent material which was positive for tubercle bacilli on culture and guinea pig inoculation. Tuberculin skin test was positive. Sputa and gastric cultures were negative for acid-fast bacilli. He left the hospital against advice in June 1949 due to certain domestic difficulties.

Marked fluctuant swelling of the left knee and leg were noted upon admission here and aspiration secured purulent material which was consistently positive bacteriologically for tubercle bacilli. Roentgenograms of the knee revealed a destructive process of the joint cartilage and bony margins of the tibia. Arthrodesis of the knee joint was done on September 23, 1949 with an adjunct course of streptomycin given during and after the surgical period. Spine survey and bacteriologic studies of the urine have been negative. The chest wall sinus has closed under strepto-

mycin therapy, but future surgery may be necessary to excise this tuberculous focus. There has been no evidence of parenchymal pulmonary disease, although the area of pleural involvement remains essentially unchanged at the left base.

Comment: This patient received no treatment for his initial pleurisy with effusion. Within six months there was evidence of tuberculous involvement of the bony thorax and of the left knee joint. Surgery of the left knee was necessary due to the destructive involvement, which will leave this still young man with considerable disability.

Our approach at this hospital to the treatment of these effusions after the acute phase provides at least six months of bed rest, under sanatorium conditions, limiting activity to one bathroom privilege per day. Those with extensive effusions or evidence of activity which does not rapidly subside are treated with the same period of rest, but dated from the time the process began to show definite evidence of inactivity. Chest roentgenograms and blood sedimentation rate values are secured at six week intervals during this period, as well as bacteriologic study of sputum and gastric expressions at monthly intervals. The patients are also carefully observed for any evidences of extrapulmonary tuberculosis. At the end of the six month period the patient is reevaluated and may be allowed a program of gradual reambulation over a period of three to four months, or may be required to take additional bed rest if his progress has not been entirely satisfactory. Gradual return to full activity is recommended over a period of six months following discharge from the hospital, and the patient is recalled at intervals of two to three months for reexamination for the first year following discharge and at gradually lengthening intervals for at least five years. This is essentially the usual sanatorium program and its long term implications for the patient make it most difficult for the physician effectively to treat these patients at home, unless exceptional circumstances exist. Although this program has been in effect at this hospital for only about three years and complete follow-up data are not available, it is estimated that less than 5 per cent of those patients treated and effectively cooperating on this regimen have subsequently developed any evidence of pulmonary or extrapulmonary tuberculosis.

It is not an easy task for the physician to recommend a long period of inactivity to a patient with "idiopathic" pleural effusion, especially when the diagnosis must be based on the clinical picture and a positive tuberculin skin test, without bacteriologic evidence with which the patient can be confronted and persuaded. The temptation to "take a chance" is sometimes difficult to resist in such an instance, although few physicians would recommend such a course were the patient found to have active minimal pulmonary

tuberculosis instead of pleural effusion. The prognosis and clinical significance of post-primary pleural effusion is essentially that of such a pulmonary lesion, and the treatment in each instance should be little different to achieve optimum results. Thorough and repeated explanation to the patient and his family of the nature and possible consequences of the effusion must be made to aid them in reaching the proper decision. The social, domestic and financial implications for a patient who must spend six or more months in a sanatorium for the treatment of "idiopathic" pleural effusion requires firmness and conviction on the part of the physician who makes that recommendation. When there is question or choice of diagnosis, often prompted by the physician's own lack of conviction, the patient will usually apply the diagnosis of lesser consequence to his case.

The fact that pleurisy with effusion occurs most frequently in the late adolescent and early adult age groups makes adequate treatment vital, although patient resistance to treatment is also high in this group. The benefits resulting from adequate care in this group are obvious. Sanatorium physicians have an acute awareness of the problem of pleural effusion, and little difficulty should be encountered in securing treatment for these patients. Should the patient fail to be convinced of the necessity for continued inactivity after subsidence of the acute phase of the effusion, every effort should be made to have him return at two month intervals for reexamination, including careful fluoroscopy or chest roentgenogram, for a period of at least six months following the effusion and at gradually lengthening intervals for the next five years. Local or county health units are also available for the continued follow-up of these patients upon referral, and such observations may be invaluable in detecting early pulmonary or extrapulmonary activity from the standpoint of both the patient and the public.

This paper has attempted to present some aspects of the problem of post-primary or idiopathic pleural effusion and its significance as a manifestation of an active tuberculous process. The conclusion is inescapable that the practicing physician stands in a most important position with relation to the recognition and adequate treatment of the patient with pleural effusion. Physicians active in tuberculous work who have seen patients admitted for the treatment of sometimes far advanced pulmonary or extrapulmonary disease and whose history included a previous episode of inadequately treated pleural effusion cannot but feel that an important aspect of preventive medicine has been neglected and a valuable clinical sign overlooked.

SUMMARY

1) Idiopathic pleurisy with effusion in the tuberculin positive individual should be considered a manifestation of tuberculosis in every instance, despite negative cultures of the aspirated fluid, and offers a sign of valuable clinical significance to the physician.

2) The age group involved makes recognition of the tuberculous etiology an important tuberculosis control factor, with obvious social and economic implications for the group.

3) A high incidence of pulmonary and extrapulmonary tuberculosis follows inadequately treated pleurisy with effusion, chiefly within the first two years following the effusion.

4) Sanatorium treatment, similar to that employed for minimal active tuberculosis, is strongly recommended in every case, with an observation period of at least five years following the effusion.

5) Control of the effusion by adequate aspiration is indicated to avoid pleural changes and subsequent impairment of pulmonary ventilatory function as an added complication.

RESUMEN

1) La pleuresía con derrame idiopática en individuos tuberculino-positivos debe considerarse indicación de tuberculosis en todo caso, no importa si los cultivos del líquido aspirado sean negativos, y es, para el médico, un signo de valioso significado clínico.

2) Debido principalmente a la edad del grupo afectado, el reconocimiento de la etiología tuberculosa de ese estado es un factor importante en el control de la tuberculosis, con claras implicaciones sociales y económicas para ese grupo.

3) La pleuresía con derrame tratada inadecuadamente conduce a una elevada incidencia de tuberculosis pulmonar y extrapulmonar, especialmente en los dos años que siguen al derrame.

4) Se recomienda vehementemente que todo caso reciba tratamiento sanatorial semejante al que se emplea en casos de tuberculosis mínima activa, con un período de observación de, por lo menos, cinco años después del derrame.

5) Se indica el control del derrame mediante la aspiración adecuada para evitar la complicación de alteraciones pleurales que causen daño subsiguiente a la función ventilatoria del pulmón.

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Dust Inhalation in Relation To Pulmonary Disease*

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Everyone is inhaling some dust with almost every breath taken, but the results of this dust upon the lungs is considered part of the natural process of aging when it occurs outside of his occupation. The relationship of dust inhalation to pulmonary disease is therefore usually considered only from the point of view of industrial exposure. Observations on the effect of dusts in industry have consequently been limited largely to those pathological processes which can be clearly differentiated from pulmonary diseases of non-occupational origin. To these characteristic changes in the lungs produced by dust, the term pneumoconiosis has been applied.

Diagnostic Factors in Pneumoconioses

In order to establish the diagnosis of pneumoconiosis, two factors must be present: 1) pulmonary pathology which might have been produced by exposure to a particular dust, and 2) an occupational history of exposure to that dust. The chest physician is generally in a good position to evaluate the first factor, through the medium of signs, symptoms, x-ray inspection and laboratory tests. In determining the second factor, he is often handicapped by his paucity of knowledge of the nature of his patient's work and the materials handled. Most physicians are aware that a rock miner or stone cutter may be exposed to free silica in amounts capable of causing silicosis. They may not be aware, however, that a worker in a soap factory, which includes in its products scouring powders, may be handling large quantities of silex, which is almost pure pulverized silica. In other instances, the etiology of the pulmonary pathology may not be so readily recognized because the physician is unaware of the more obscure effects upon the lungs of a material such as talc or bagasse.

Another factor which makes it difficult to recognize the importance of an industrial dust exposure in the pathogenesis of a pulmonary disease is the close resemblance which frequently exists

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between that disease and some other pulmonary pathology of non-industrial etiology. When the x-ray picture is characteristic, as in an obvious case of nodular silicosis, the physician is apt to inquire carefully into the worker's occupation, and to enlist the aid of industrial hygienists or other experts in an effort to establish a dust etiology. When the clinical and sometimes even the pathological findings are almost identical with some non-occupational disease of the lungs, however, he is not so likely to seek far afield for an occupational exposure. It was not until the unusual incidence of workers dying from what was presumed to be Boeck's sarcoid in a plant manufacturing fluorescent lamps was noted, that the toxicity of one of the materials which they were handling was even suspected, and that the identity of chronic pulmonary granulomatosis due to beryllium was established.[1] Recognition of the dust etiology is even more difficult when the pathology is identical with that of a non-occupational disease, as for instance the primary lung carcinoma seen with increased frequency in chromate workers.[2]

Another way in which dust inhalation may affect pulmonary disease is by aggravation of a pre- or co-existing non-occupational disease. Today, the fact that silicosis predisposes a worker to tuberculosis, and renders that tuberculosis much more severe, is well established. We are just becoming aware, however, that some of the more innocuous dusts may adversely affect the course of tuberculosis and other pulmonary infections.[3] It is no longer considered good practice for an individual with arrested tuberculosis to return to work in any dusty environment. We all too frequently, however, see workers with chronic bronchitis, pulmonary emphysema or even bronchiectasis who are permitted to work in an extremely dusty atmosphere. Even the increased coughing induced by a dust which is slightly irritant to the upper respiratory passages, or necessary to clear these passages of the accumulated particles, may be sufficient to aggravate a chronic pulmonary disease.[4]

Over and above all of these specific aspects is the general effect of dust on the aging processes of the lung. I would like to quote an observation made by Dr. Edgar Mayer, in an article[5] he published a few years ago: " respiratory infections and general dust exposure eventually provoke pulmonary changes. There exist only differences in degree, not in kind, between the so-called normal amount of pulmonary fibrosis so prevalent in the general population and those severe fibrotic processes which destroy the lungs of workers in industries wherein exposures exist to more concentrated and continuous effect of the same agents present in greater dilution in the atmosphere of industrial centers."

Dust Characteristics

A pre-requisite to the understanding of the effects of dust inhalation upon the lungs is a knowledge of the type of material under discussion. We have chosen to cover in this paper all forms of solid particulate matter generated in the course of industrial operations, because in so many instances their effects are similar or even identical. Fibers and fumes as well as dusts have therefore been included. Since some uncertainty exists as to the exact meaning of these terms in industrial hygiene, we shall start with a few definitions. The term dust is applied to the solid particles produced by handling, cutting, crushing, grinding or pounding organic or inorganic materials such as rock, ore, metal, coal, wood, grain, etc. Fibers are the particles similarly produced from organic or inorganic material composed of thread-like or slender elements such as cotton, wool, fur, bagasse or asbestos, and are also created in such operations as stripping, spinning and weaving. Fume is a term limited to the solid particles created by condensation from a gaseous state, generally after volatilization from molten metals, and often accompanied by a chemical reaction such as oxidation. Contrary to general usage, it does not refer to condensations to a liquid droplet form, which are called mists, or to a uniform gaseous dispersion, whether visible or invisible, which is referred to as a vapor or gas.

The common denominator of all these materials is thus the fact that they are present in the atmosphere as solid particles. An important characteristic of these particles is their size.[6] It has been shown both theoretically and experimentally that on inhalation those which are too large do not reach the lungs, but are filtered out in the upper respiratory passages. Particles which are too small, on the other hand, do not settle out, and are therefore theoretically not retained in the alveoli but are re-exhaled. The question of the innocuousness of these sub-microscopic particles has recently been open to question. It is a generally accepted principle, however, that the particles exert their greatest deleterious effect upon the lungs when they are between 0.5 and 3 microns in diameter.

The other important factor determining the reaction of a dust upon the lungs is its composition, that is, its chemical and physical characteristics.[7] Where it is a mixture of several different compounds, such as the dust created in a granite quarry, the percentage of the most active ingredient (in this instance free silica) is of the utmost importance. Even where the mixture is man-made and not a natural product, its composition has to be taken into consideration. For example, the sand used in an iron

foundry may consist of almost pure silica, but the dust released in a shake-out operation will have a much lower silica content because a large part of it comes from the iron oxide particles separated from the surface of the casting. The particle structure also appears to play a role: crystalline silica has long been considered a far more active substance than the amorphous form. Fumes from a melting operation are frequently much more reactive than the same material created as a dust by grinding or crushing. In some instances even the shape of the particles has significance, particularly when their effects are dependent to a large extent upon local mechanical irritation.

Protective Mechanisms

There are a number of mechanisms by which the lung parenchyma is protected from inhaled dust.[7] Many of the particles may be filtered out by the coarse hairs guarding the entrance to the nose, or trapped by the moist walls of the turbinates. Particles deposited on the surface of the mucous membranes of the trachea and bronchi are carried back towards the pharynx by the wave-like vibrations of the cilia, and also by the cough reflex induced by the irritation to the lining membranes.

Particles which succeed in passing these barriers and gain entrance into the alveoli are ingested by macrophages which arise from the alveolar walls and are commonly referred to as "dust cells." Some of these phagocytes, laden with dust, may pass up into the bronchioles and eventually be carried off in the sputum; the others pass through the walls and into the regional lymphatics. Some of the latter are arrested locally in the peribronchiolar tissue, but the remainder pass onward into the peribronchial and perivascular lymphatics, and are finally trapped in the lymph nodes at the root of the lung.

Types of Pathology

The type of pulmonary pathology which may be caused by the inhalation of a specific dust is determined by the manner in which this lung cleansing mechanism is disturbed, and by the type of reaction which results. Probably the best known is the fibrotic reaction produced by exposure to silica and similar materials.[8] This reaction represents a specific cellular response to the material. The particles engulfed by the dust cells stimulate the production of fibroblasts in any area where they are congregated; and these fibroblasts are eventually replaced by dense fibrous tissue. In the case of dusts other than silica, this fibrosis is usually fairly generalized; but with silica, it tends to nodular formations distributed along the lymphatics. In either case, the net effect is to make

the lungs less elastic, increase their bulk while decreasing their capacity, and decrease pulmonary circulation and aeration of the blood.

Less characteristic is the action of those dusts which act as general irritants,[9] particularly on the respiratory passages, but do not exhibit a specific fibrosing action. Included in this category are most of the organic dusts. Workers first exposed to them respond by sneezing and coughing, but usually quickly become acclimatized so that the irritant action is no longer found troublesome. Continued inhalation of these dusts, however, may result in chronic inflammatory changes in the mucous membranes with secondary hyperplasia or atrophy. Degenerative changes have also been noted, with disappearance of the ciliated columnar epithelium and its replacement by a cuboidal or squamous form.[10] The chronic cough induced by these irritants may also be responsible for emphysema and other secondary changes in the lungs.

In addition to this generalized irritant action, certain dusts may elicit a specific inflammatory response.[9] This may be of a chemical nature, as in the case of beryllium or Thomas slag, or may be infectious, due to bacteria or fungi carried in by the dust. In both instances, the pathology of the response depends upon the material producing it, and may be acute or chronic, reversible or permanently damaging. With some materials, for instance beryllium, the pathology is quite characteristic. With others, particularly those transporting micro-organisms, it may be indistinguishable from non-occupational infections of the pulmonary tract, and only a careful investigation of the patient's occupation will elicit the offending material.

Even when the dust particles exert no irritant action whatsoever, there may be slight pulmonary changes due to their mechanical effects.[11]

Pulmonary allergy is a type of response observed with certain organic dusts,[12] particularly those of plant or animal origin. The picture is one of a typical asthma, and only the occupational history differentiates it from identical reactions so commonly seen from pollens or house dusts. The distinction often can only be made by patch testing or similar procedures, which will demonstrate that the responsible antigen is present in the man' occupational rather than non-occupational environment.

Primary carcinoma of the lung has at one time or another been ascribed to a great many of the industrial dusts produced in industry. Proving or disproving the carcinogenic properties of any particular material is often an extremely difficult procedure, because the pathology in no way differs from that of a lung cancer of unknown etiology. Merely demonstrating the co-existence

of cancer and some other pulmonary disease such as silicosis, is not sufficient, since there is no reason why the incidence of malignancy in silicotics should be any lower than it is in non-silicotics. The only satisfactory proof of such carcinogenicity is the uniquivocal demonstration of an incidence of cancer in workers exposed to a particular dust which is sufficiently higher than that of a comparable group of non-exposed workers to have statistical significance. Great care must be taken in selecting the control group to insure that all extraneous factors, such as age distribution, sex and non-industrial environment, are identical. The high incidence of lung cancer in the uranium mines of Schneeberg and Joachimsthal has been known for some time.[1,3] More recently, an increased incidence of pulmonary malignancy has been demonstrated in workers exposed to chromate dusts,[2] although the statistical significance of the data which have been collected on this material is still being investigated. Both silica and asbestos have on many occasions been indicted as predisposing to lung cancer; but in the case of silica, it has never been demonstrated statistically, while accumulating evidence points more and more strongly to asbestos as a carcinogenic agent.[14]

Pulmonary Disease Due to Silica

Having presented the general types of pulmonary pathology which may be produced by dusts, I would like to devote the remaining time to a brief description of the specific pulmonary effects produced by certain materials. As has been previously pointed out, undoubtedly the most important of these is silica. This is the oxide of the element silicon, and is widely distributed, both free and combined, in the earth's crust. Crystalline silica occurs pure as quartz and as beach sand, and is also scattered in varying percentages throughout many forms of rock, such as granite, marble and sandstone. Dusts containing free silica can be created industrially in a multitude of ways, such as drilling and blasting operations in the course of mining and quarrying, cutting and shaping of stone, rock crushing, sand blasting or any other operations in which quartz, sand or silica-containing rock is processed. The disease[8] is characterized anatomically by generalized fibrotic changes and the development of miliary nodulation throughout the lung fields, and clinically by cough and progressive shortness of breath. Chest x-ray films show at first an exaggeration of the lung markings and lymph node enlargement, which is followed by nodulation, and finally by coalescence and conglomeration. Tuberculosis may be super-imposed at any stage, and is believed by some to be present in all areas where coalescence has taken place. As a rule, there is no fever or weight loss in

simple silicosis, and these signs may be indicative of a complicating tuberculosis. The patient tends to go downhill very rapidly with the development of an active tuberculous lesion.

Many observers have been of the opinion that silicosis could be caused only by the crystalline form of silica, but evidence is accumulating to the effect that the amorphous form as well is capable of producing pulmonary damage. Observations upon the effects of amorphous silica[15] have been made largely on workers exposed to diatomaceous earth, which is a light fluffy material formed by the accumulation of skeletons or shells of diatoms. It has a wide use in industry as filters, fillers and absorbents. In contrast to crystalline silica, it produces fibrosis of the lungs without discrete nodulation. The fibrosis is much more marked when the exposure is to calcined material, during which process microcrystals of chrystobalite may be formed. Disability appears to be less marked than with silica, and the fibrosis seems to diminish rather than enhance susceptibility to tuberculosis.

Another possible example of pulmonary damage due to a non-crystalline form of silica occurs in workers fusing bauxite in electric furnaces in the manufacture of alumina abrasives.[16] The fumes given off in this operation consist[17] of 25 to 40 per cent silicon dioxide and 40 to 60 per cent aluminum oxide, together with small amounts of iron oxide and numerous other impurities. Under the electron microscope they are revealed as fused particles varying in size from 1/100 to 1/2 micron in diameter. A high percentage of the workers exposed to these fumes have developed cough with expectoration, weight loss, anorexia, tightness in the chest, and dyspnea on exertion. X-ray inspections show a lace-like or granular increase in the lung markings, beginning at the apices. These gradually extend to involve the entire lung fields, and may be accompanied by pleural adhesions causing distortion of the thoracic contents. Spontaneous pneumothorax is a common complication. While the aluminum oxide has generally been advanced as the etiological agent responsible for this disease, it seems quite possible that this may be a response to silica fume with a particle size far lower than that generally considered injurious, especially since more than one form of silica have been shown to be damaging to the lungs, while aluminum oxide has always been considered a non-fibrosing agent.

Silica, when present only in combined form as a silicate, has usually been regarded as relatively inert. Considerable evidence, however, has been accumulating against this concept. Probably the best known of the silicates producing severe pulmonary damage is asbestos.[18] This is a mineral silicate occurring in the form of long fibers, which renders it capable of being carded, spun, and

woven into threads and cloth, or bonded with cement into building shapes. Inhalation of these fibers in the course of mining or processing asbestos has been shown to be responsible for the development of progressive pulmonary fibrosis with diffuse thickening of the alveolar walls. The outstanding symptoms are dyspnea and dry cough. Emphysema, pulmonary infections, and secondary cardio-vascular changes due to increased pulmonary resistance are the most common sequelae. Chest x-ray films show a "ground glass" haziness, rather than the reticulation and nodulation of silicosis.

Another combined silicate which has been shown to be not completely inert is talc, a hydrated magnesium silicate used extensively in its powdered form as a dusting agent. It may contain variable percentages of free silica; and when these are high, the classical picture of silicosis has been observed in workers mining, crushing, grinding or otherwise handling it. Even when it contains under 1 per cent free silica, however, as is usually the case, the dust, when inhaled, is capable of producing a fine diffuse pulmonary fibrosis similar to asbestosis.[19] It tends to be disabling, and is frequently accompanied by dyspnea, cough and fatigue. In addition, deposits of x-ray opaque material on the pleural surfaces in the form of plaques have been observed.

Still another silicate showing definite effects upon the lungs is mica, which is a double silicate of aluminum and either potassium or magnesium. This mineral, because it splits into thin sheets which are quite transparent, and have a high dielectric constant, has innumerable uses in industry, particularly in the manufacture of electrical equipment. For some time, it has been believed that the chest pathology so prevalent where it is mined was due to the free silica present in the rocks in which mica deposits occur. Even among workers exposed solely to pure mica dust in grinding operations, however, there has been observed[20] a high incidence of increased pulmonary fibrosis, with cough and dyspnea. The signs and symptoms are the same as those occurring in silicosis, but less severe. X-ray films show a fine granulation of uneven density with coalescence of the lesions in more advanced cases.

In all these exposures, the common denominator has been silica, whether free or combined. Recently, however, carborundum, which is an almost pure silicon carbide containing less than 1 per cent free silica, has been suspected of being an agent capable of causing pulmonary changes identical with silicosis.[21] This has been explained theoretically by the possible oxidation of the material in the lung. This may be the explanation for the occasional occurrence of silicosis among workers using carborundum grinding

wheels, which have been considered a completely "safe" substitute for the far more hazardous sandstone wheels.

Pulmonary Diseases of Non-Silicotic Origin

The pulmonary changes seen in coal miners has long been attributed to the free silica content of the shale through which they had to dig to get at the coal. Recent large scale studies in Wales have indicated,[22] however, that exposure to very heavy concentrations of coal dust with a negligible percentage of free silica, such as occurs among the coal trimmers on the docks, leads to a form of pneumoconiosis differing from the anthraco-silicosis of miners. There is a massive fibrosis of the lungs with nodular deposits of anthracotic pigment scattered throughout. The principal symptoms are due to the marked secondary emphysema, and the cardiac changes produced by pulmonary hypertension. Susceptibility to tuberculosis is increased. The x-ray picture is one of reticulation rather than nodulation, because of the lack of opacity of the nodules.

Specific pulmonary pathology has also been shown to be produced by exposure to fumes and dusts of certain of the metals, notably beryllium and cadmium. Both these substances actually are systemic poisons, but since industrial exposure to them occurs primarily by inhalation, the principal pathology is usually present in the lungs.

Beryllium is responsible for two types of respiratory disease.[23] One is an acute inflammatory reaction varying from a mild pharyngitis or bronchitis to a massive pulmonary edema, which occurs principally among workers exposed to soluble salts in the beryllium refining industry. The other is a chronic pulmonary granulomatosis developing after a delay of several months to years, which occurs primarily among workers exposed to dusts and fumes of the metal, oxide, and certain complex silicates (fluorescent compounds). It is characterized by a nodular fibrosis giving a characteristic x-ray picture, and a diffuse thickening of the alveolar walls. The outstanding symptoms are dyspnea, fatigue, anorexia, severe weight loss and intractable cough. The mortality is high, and some degree of permanent disability remains among nearly all those who survive. Interrelations between the acute and chronic forms, and the occurrence of an intermediate subacute type, indicate that they are probably all widely different manifestations of the same disease process.

The pulmonary pathology due to cadmium[24] is generally encountered when workers unwittingly create cadmium fumes without adequate protection: for example, in flame cutting or welding

cadmium plated iron. It first causes a cough and dryness of the throat, which then progresses to severe constricting chest pain and dyspnea, dizziness, chills and prostration. The pathological picture is that of pulmonary congestion and edema, with interstitial pneumonitis, hemorrhage and cellular infiltration.

The term siderosis[25] has been applied to a benign pneumoconiosis due to exposure to dust and fumes of iron and its oxides, usually seen among hematite miners, welders and other iron workers. Pathologically, siderosis consists of a deposition of phagocytized iron particles distributed in nodular fashion along the lymphatics. Outside of the mechanical effects of excessive pulmonary accumulation previously discussed, its importance lies chiefly in the necessity of differentiating it from silicosis, with which it had frequently been confused in the past, particularly among foundry workers. The nodules in siderosis are more discrete and sharply defined on x-ray, and there is no tendency to confluent nodulation or hilar enlargement.

Organic Dust Diseases

A few materials of organic origin have been found to be responsible for specific types of pulmonary pathology. Notable among these is bagasse,[26] which is the residue of sugar cane after extraction. This material has been extensively used in the manufacture of insulating board and other building materials. It shreds readily when handled dry, with the production of a fibrous dust. A high percentage of workers exposed to these fibers have developed, after about two months, an acute bronchiolitis with high fever, extreme dyspnea, productive cough, weakness and weight loss. X-rays show scattered miliary shadows throughout the lung fields which may go on to a confluent pneumonia. The disease usually clears up, but may be fatal or result in chronic fibrosis or bronchiectasis.

Both acute and chronic pulmonary diseases have been reported among cotton workers. The former[27] consists of an acute febrile illness with productive cough and dyspnea, resembling an acute bronchitis. It usually resolves completely, but may occasionally result in chronic bronchitis. It is believed to be due to the dust of the fungi or bacteria which grow on damp, unsterilized cotton. The chronic disease,[28] known as byssinosis, consists of a progressive fibrosis, usually associated with emphysema and bronchiectasis, which develops after many years of inhalation of cotton fibers. It is not yet known whether it is a specific fibrotic response, an allergic reaction, or the end result of repeated subclinical acute infections.

SUMMARY

There are a number of types of pulmonary pathology which can be caused by the inhalation of excessive quantities of particulate matter, varying from specific fibrotic reactions with a characteristic picture to an increased incidence of a form of pathology usually considered non-industrial in origin. Size, composition and structure of the particles are all factors determining the nature of the response. Pathological reactions generally result when the capacity of the filtering and phagocytizing mechanisms of the respiratory tract are exceeded. These reactions may be fibrotic, inflammatory, degenerative, allergic, carcinogenic or merely mechanical impairment of function.

The best known cause of pneumoconiosis is free crystalline silica, but amorphous silica, silicates, and even silicon carbide have been shown to exert deleterious effects. Coal dust, certain metals, and a few organic compounds, have also been indicated as the cause of specific lung pathology. A careful evaluation of both the clinical picture and the occupational history is necessary in every case of chronic pulmonary disease to rule out a possible etiological or aggravating factor in the patient's working environment, and to ensure an optimum prognosis by eliminating all future exposure to any harmful atmospheric agents found.

RESUMEN

La inhalación de cantidades excesivas de particulas de materia puede causar ciertos tipos de alteraciones pulmonares patológicas, que varían de reacciones fibrosas especificas, con un cuadro característico, a una forma patológica, de incidencia creciente, que generalmente no se considera ser de origen industrial. El tamaño, la composición y la estructura de las particulas son factores que determinan la naturaleza de la reacción. Generalmente resultan reacciones patológicas cuando se excede la capacidad de los mecanismos de filtración y fagocitosis del aparato respiratorio. Estas reacciones pueden ser fibrosas, inflamatorias, de degeneración, alérgicas, carcinógenas o, solamente, impedimentos mecánicos de la función.

La causa más conocida de la neumoconiosis es la silice cristalina libre, pero se ha demostrado que la silice amorfa, los silicatos y aún el carburo de silicio pueden causar efectos nocivos. Se ha sospechado que el polvo de carbón, ciertos metales y algunos compuestos orgánicos también causan cambios patológicos especificos del pulmón. Es necesario avaluar cuidadosamente tanto el cuadro clínico como los datos de las ocupaciones en todo caso de neumopatía crónica a fin de determinar si existe un posible factor etio-

lógico o agravante en el ambiente de trabajo del paciente, y para asegurar el mejor pronóstico posible mediante la eliminación de la futura exposición a cualquier agente atmosférico nocivo que se haya descubierto.

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The Respiratory Effects of Volatile Substances*

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The title of this paper would suggest a wide variety of volatile substances which would number perhaps several hundred. For the purpose of this discussion consideration will be given to gases, vapors and fumes as opposed to dusts, as they affect the respiratory tract. It is difficult to arrive at a completely satisfactory classification of such substances since they possess many varied physical characteristics, such as different boiling points, volatilities, solubilities, etc. In addition consideration should be given to the inherent toxicity of the substances, and their locus of action in the body.

Probably the most generally accepted classification of irritant gases is that given by Henderson and Haggard in their monograph on "Noxious Gases."[1] They classify the irritants into subgroups based on the principal sites of action in the respiratory tract. This classification with some modification will serve the present purpose very well as it can be used to cover the range of volatile substances to be discussed, namely gases, vapors and fumes. Examples will be given in each group.

I. *Volatile substances with marked effect on the respiratory system, more definite than the systemic effects which may be produced:*

A) Substances acting primarily on the upper respiratory tract. These include a number so immediately irritating to the mucous membranes, even in far less than lethal concentrations, that strangulation would usually occur with possible edema of the glottis before they could be deeply inhaled. Examples: Ammonia, Hydrochloric acid gas or mist, Sulphuric acid vapor or mist, Acetic acid, Hydrofluoric acid gas or mist, Formaldehyde, Chromic acid mist.

B) Substances acting on the upper respiratory tract but with action often extending to deeper areas. When present in extremely high concentrations they also may cause strangulation, preventing deep inspiration; but in lower concentrations they may be inhaled deeply enough to damage deeper lung tissue. Examples: Sulphur dioxide, Chlorine, Bromine, Iodine, Aldehydes, Allyl alcohol.

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C) Substances acting primarily on lung tissue and to a much less degree on upper and middle respiratory tract.

Some of these substances have rather marked acute effect on the upper respiratory tract but the danger in their inhalation is severe but often delayed action on the alveolar areas of the lung. Examples: Oxides of nitrogen, Ozone, Phosgene, Phosphorus trichloride and phosphorus pentachloride, Arsenic trioxide, Ethylene oxide, Nickel and other carbonyls, Ketene, Cadmium fumes, Beryllium in combination with certain acids.

To Henderson and Haggard's classification might be added another:

II. *Volatile substances without marked effect on the respiratory passages.* These are mentioned largely for exclusion:

A) Substances causing possibly transient irritation but without noteworthy systemic effects. Examples: Alcohols, Ethers, Esters, Ketones, Hydrocarbons, aliphatic of paraffin and olefin series, (Petroleum products, ethylene and related hydrocarbons).

B) Substances often causing even fatal systemic poisoning but usually without any noteworthy effect upon the respiratory system. Examples: Aniline, Cyanogen compounds, Carbon monoxide, Carbon disulphide, Arsine, Phosphine, Allyl chloride, Chlorohydrins, Hydrocarbons, aromatic, Hydrocarbons, chlorinated.

Irritating gases and vapors differ widely in chemical and physical properties. They have one physiological property in common, namely, they induce inflammation in the tissues with which they come into direct contact. As a result of this contact an inflammatory reaction may occur particularly in the mucous membranes of the respiratory tract, usually in the conjunctiva of the eyes and often but not always in the skin.

The inflammation or irritation caused by these materials is not the same as that produced by simple chemical corrosion. The inflammation develops from the disturbances in normal vital processes in the tissues such as coagulation, liquefaction, dehydration or some other injury. The type of direct injury caused by the gas or vapor is often too slight to be seen and depends upon the chemical nature of the irritant. The changes which may ultimately follow are often independent of the nature of the initial injury.

The initial reaction of tissue to the irritants with which they come in contact may be either chemical or physical. The effect of an irritant gas or vapor, except in most unusual instances of overwhelming concentrations, is not simple and direct corrosion. They act in such extreme dilution that such gross effects are not

usually involved. When actual chemical corrosion does occur to any extent the result may be almost immediate shock.

Sunburn can be cited as an example for comparison to demonstrate the general process of inflammation as induced by an inhaled irritant. In sunburn the irritation is due to the actinic rays of the sun and the initial injury to the skin is invisible. The burn appears subsequently as the vital reaction of inflammation and in a degree determined by the extent of the initial exposure.

There is no apparent correlation between the similarity of action of irritating vapors and the symptoms produced by exposures. The differences in symptoms are mainly due to differences in localities at which the irritants act. Some irritants act primarily upon the upper respiratory tract and induce rhinitis, pharyngitis and laryngitis. Others extend their action to the bronchi and cause bronchitis and bronchopneumonia while still others act chiefly on the lungs themselves, causing pulmonary edema, pneumonitis or pneumonia.

The location in the respiratory system exposed to an irritant gas or vapor influences the symptomatology and pathology. As an example exposures to ammonia gas in high concentrations are followed by intense congestion and swelling of the upper respiratory passages and possibly rapid death from spasm or edema of the glottis or larynx. If the immediate effects are survived there may be little or no pulmonary damage, since the deeper structures of the respiratory tract are not reached and therefore are not injured. Phosgene and nitrogen dioxide even in concentrations which may later be lethal, cause comparatively little immediate irritation of any of the mucous membranes of the respiratory tract but induce pulmonary edema through their action on the deep lung structures.

Referring to the outline which has been presented,

I. *Volatile substances with marked effect on the respiratory system, more definite than the systemic effect which may be produced:*

A) Substances acting primarily on the respiratory tract:

Ammonia gas presents a good example of this group. It is a colorless gas with a specific gravity of 0.597 times that of air. It is easily liquified and is extremely soluble in water with which it forms ammonium hydroxide. The aqueous solution yields gas on exposure to air. Because of its extensive use, exposures are not uncommon. Since ammonia is highly irritating it possesses ample warning powers and accidents due to exposures while fairly frequent are rarely serious. It acts violently upon the upper respira-

tory tract but does not reach the lower respiratory tract producing changes in the lung itself except under rare circumstances.

Hydrochloric acid (hydrogen chloride) is a colorless gas with a specific gravity 1.269 times that of air. On exposure to air this gas forms a dense white fume from the condensation of atmospheric moisture and the formation of hydrochloric acid in minute droplets like steam. Since the gas is rarely encountered in the anhydrous state the irritation is caused by these droplets like steam. The toxicity of hydrochloric acid as droplets is less than that of hydrogen chloride since they have lost their dehydrating action. The location of action of hydrochloric acid on inhalation is chiefly confined to the upper respiratory tract as in the case of ammonia.

Sulphuric acid is a liquid at ordinary temperatures and because of its high boiling point of 330 degrees C. it gives off no appreciable fumes. When it is heated it gives off dense and very irritating fumes. When hydrogen is evolved from sulphuric acid solutions acting on a metal, bubbles of gas carry finely divided spray of acid in the air. Sulphuric acid mists or vapors confine their action to the upper respiratory tract affecting the trachea as well as the nose, throat and glottis.

Acetic acid and *acetic anhydride*. Vapors of acetic acid are irritating to the upper respiratory tract. Acetic anhydride in contact with water or water vapor is hydrolyzed to acetic acid. Acetic anhydride is very irritating to the upper respiratory tract due to its contact with the moist mucous membranes with resulting hydrolysis.

B) Substances acting on the upper respiratory tract but with action often extending to deeper structures.

Sulphur dioxide would be in this classification and has been frequently mentioned recently as it has been considered one of the principal active agents in smog experiences in such places as Donora, London and Los Angeles. Sulphur dioxide is constantly discharged into the air of cities by the burning of coal containing sulphur and from the effluent of oil refineries. In the presence of moisture, the dioxide is oxidized and forms sulphuric acid. It is a colorless gas and has a specific gravity 2.23 times that of air. The gas is irritating to the eyes, nose and throat and in addition irritates the deeper structures of the lung. It is so irritating to the upper respiratory passages that those exposed usually withdraw from the excessive exposure before the deeper structures are affected. Massive exposures are capable of producing edema of the lung. Recovery from exposures results in no permanent disability. Some observers have noticed a lessened tendency to colds, bronchitis or other respiratory infections among individuals who are exposed to this material in the course of their work.

Chlorine has a specific gravity of 2.47 times that of air. It is one of the more common irritating gases to which individuals are exposed because of its extensive use. Chlorine is so irritating that it has good warning powers and an exposed individual usually withdraws from the exposure before severe gassing can take place. There has been considerable conjecture as to how chlorine acts on the respiratory tract. It has been supposed that chlorine reacts with the moisture on the tissues to form hydrochloric acid and its adverse effect is due to the action of the acid. Chlorine is more toxic than hydrochloric acid and because of its relatively low solubility its locus of action in the respiratory tract is much more extensive than in the case of hydrochloric acid. A probable theory which has been advanced on the action of chlorine is that it affects moist tissues in the same way that it does moist organic material. This action is by abstraction of hydrogen from the moisture present, the liberation of nascent oxygen and then the formation of hydrochloric acid. Oxidation would thus be the major factor, which together with the action of the acid induces irritation of the tissues. If chlorine is deeply inhaled it can produce edema of the lungs.

The temporary disability from exposures to chlorine is short, lasting, as a rule, a few days at most. It has been stated that chronic chlorine poisoning is unknown and permanent disability due to chlorine gassing has not been observed.

Bromine and *iodine* would have effects similar to those of chlorine.

The *aldehydes* have anesthetic properties but their action in this respect is largely masked by the more intense irritant effect upon the surface tissues of the respiratory tract. The lower members of the aldehyde series are very soluble in water and for this reason act principally upon the upper respiratory tract while the higher members, especially acrolein, are less soluble and act in the deeper parts of the respiratory tract.

C) Substances acting primarily on lung tissue and to a much less degree on the upper and middle respiratory tract.

An example of an irritant which would be representative of this group was reported by Dr. H. S. Van Ordstrand and others as "Beryllium Poisoning."[2] The condition was later defined at the conference on beryllium at Saranac Lake as acute pneumonitis in beryllium workers in contrast to the chronic condition due to exposures to beryllium dust principally in the form of zinc beryllium silicate. Some abstracts from this article are as follows:

The cases reported were encountered in employees associated with the extraction of beryllium from beryl ores. During the process hydrofluoric acid and sulphuric acid were used with resulting

fumes in the atmosphere of these two acids in combination with beryllium. In this study the highest incidence of the disease occurred in those individuals who were exposed to oxylfuoride and sulphating phases of the processing of the ore. One hundred and seventy cases were reported, which included such conditions as dermatitis, chronic skin ulcer and inflammatory changes of the respiratory tract. The severest manifestation was a diffuse pneumonitis of which 38 cases were noted and resulted in five deaths.

In the cases of pneumonitis, the following symptoms were noted: Cough, with occasional blood streaked sputum, substernal burning pain, shortness of breath, cyanosis in most cases, abnormal taste, anorexia with some weight loss and increasing fatigue. In each instance the onset was insidious and was characterized by a dry cough and occasional dull substernal burning pain. The pain tended to disappear after one or two weeks but the cough progressed in severity and there was expectoration of small amounts of blood in almost every case. Within a few days or a week after the onset of cough, these patients complained of dyspnea on exertion. The duration of the disease from onset to complete recovery varied from five weeks to four months.

The roentgenographic changes in the lung fields did not usually appear until two or three weeks after the onset of symptoms and physical signs. Changes were bilateral and diffuse in all cases and varied with the severity of the disease. In order of appearance the changes were diffuse haziness of both lungs; development of soft irregular areas of infiltration with prominence of peribronchial markings; absorption of soft infiltration and appearance of discrete large or small conglomerate nodules scattered throughout both lung fields; and clearing of the lung fields after four months.

In a review of 406 cases of acute dermatitis and pneumonitis in beryllium workers over an eight-year period[3] from 1940 through July 1, 1948, 90 cases were reported with manifestations of acute pneumonitis in which 10 deaths occurred. The recent reexamination of 20 patients who had the severe type of pneumonitis revealed no recurrent or chronic manifestations of the disease and no resultant disability. So far as is known none of the workers who had acute pneumonitis from beryllium have developed recurrences or chronic conditions such as chronic pulmonary granulomatosis.

Nitrogen dioxide. There are three common oxides of nitrogen, namely, nitrous oxide, N_2O; nitric oxide, NO; and two forms of the dioxide, NO_2 and N_2O_4, often loosely referred to as "nitrous fumes." The nitrous oxide has no irritating action and is used as an anesthetic in combination with oxygen. Nitric oxide does not exist in the atmosphere for in the presence of moisture and oxygen it is converted into the dioxide. The nitrogen dioxides are the

compounds which are irritating. While these dioxides are by no means the most toxic of the irritant gases, they are among the most insidious. The inflammation of the lungs gives rise to little pain or discomfort, but is out of all proportion to the irritation of the upper respiratory tract. These fumes have little warning power and an individual without serious discomfort may breathe an atmosphere containing a concentration of nitrogen dioxides sufficient to cause death some hours later due to the development of pulmonary edema. The delayed action sometimes preceded by a symptom-free latent period of some hours presents a special hazard.

If there is an overwhelming dosage of nitrogen dioxide fumes death occurs immediately and there will probably be no pathological changes noted at postmortem other than congestion of the lungs. In those cases in which death is delayed the lungs show on microscopic study edema of the alveolar wall as exudate into the alveolar epithelium and polymorphonuclear infiltration.

Ozone is a gas of low solubility but of intensely irritating action. The upper respiratory tract is affected but the main point of action appears to be in the lungs. The material can produce edema of the lungs probably due to its oxidizing action on the moist surfaces of the lining of the alveoli and smaller bronchi.

Phosgene is a colorless gas with a specific gravity 1.38 times that of air. In the presence of moisture, phosgene decomposes with the liberation of hydrochloric acid. Phosgene resembles nitrogen dioxide in that it causes slight immediate effects and subsequent virulent results.

Cadmium, of all the various metal fume exposures, seems to stand out as capable of producing delayed lung changes, and the lungs seem to bear the brunt of the assault from the inhalation of the fumes.[4] There is little irritation of the upper respiratory system and usually the first symptom noted is a dryness of the throat and a feeling of soreness in the chest. This is followed by cough with headache and dizziness. After 12 to 36 hours there occur severe constricting pain in the chest and marked dyspnea. The delay is comparable to that seen in phosgene and nitrogen dioxide poisoning.

It is said that on auscultation of the lungs it is rarely found that the degree of pathology is indicated by the clinical picture. Until near death, rales are conspicuously absent and breath sounds may or may not be exaggerated. Roentgenograms will often show a surprising degree of wide-spread, patchy bronchopneumonia throughout both lung fields out of proportion to what one can note on auscultation of the lungs.

Death may occur from undue exposure to cadmium fumes. A

slight exposure will cause an illness lasting only a few days. More severe exposure may incapacitate for a long time because of marked dyspnea on exertion, even though the patient is otherwise symptom-free. Ultimate recovery from even severe exposure is complete and no sequellae have been encountered.

II. *Volatile substances without marked effect on the respiratory passages.*

The majority of volatile substances, which includes solvents, are hazardous not so much because of adverse effects on the respiratory system, but because of their systemic effect after absorption through the mucous membranes of the lung and into the blood stream. As noted earlier, these substances are mentioned primarily for exclusion. This group may have anesthetic properties, acting principally on the nervous system; they may produce their effect by their adverse action on the blood-forming organs of the body; they may interfere with the handling of oxygen in the blood stream or tissues; they may affect the blood itself; they may damage vital organs such as the liver or kidneys; and they may have specific actions dependent upon the inherent toxicological properties of the substance itself.

Chronic Effects and Susceptibility to Infection

The respiratory effect from inhalation of volatile substances is essentially an acute reaction. Even in severe cases, if death does not result, complete recovery is the rule. In some quarters there seems to be an assumption that repeated exposure to respiratory irritants of a volatile nature will lead to chronic disease, or increase in the incidence of infections such as tuberculosis. There does seem to be some evidence that continued exposure to volatile irritants is one factor out of many which contribute to the high rate of acute upper respiratory infections and pneumonia noted in those engaged in certain industrial operations. At least in most of these operations such factors as extremes in temperature and humidity, presence of dust, etc., probably are of greater significance.

While the respiratory mucous membrane usually reacts quickly to volatile irritants, recovery after most exposures is prompt and complete. With repeated exposure evidence of chronic irritation may be noted but even in these cases the signs and symptoms usually disappear soon if exposure ceases. The more severe cases, as in chemical pneumonitis, in the great majority of instances recover completely with no evidence of residual damage.

As for exposure to irritant volatile substances predisposing to the development of tuberculosis, clinically there is very little evidence of this. Experimentally Gardner[5] did considerable animal

experimentation on the relation exposure to welding fumes might have on development of tuberculosis. These fumes are often acutely irritating and usually contain appreciable concentrations of oxides of nitrogen, yet the report of his study gives the following:

"Welding fumes and gases therefore cause no permanent changes in the lungs, which alter reaction to the tubercle bacillus." "Exposure to arc welding emanations is incapable of causing reactivation and spread of tuberculosis from preexisting partially healed tubercles." "Severe pulmonary irritation *per se* does not favor infection with tubercle bacilli and bring about progressive tuberculosis."

Other evidence that exposure to volatile irritants does not predispose to the development of tuberculosis or other serious lung conditions of a chronic nature is shown in the results of mass x-ray surveys of large numbers of men employed in chemical and related industries where such exposures exist. The findings in these surveys show no increase in incidence of such cases over those found in similar large groups with little or no such exposure. There are of course a few cases noted from time to time where following massive but non-fatal exposure, as for instance the oxides of nitrogen and some of the war gases, some degree of permanent disability has resulted. Such cases, to say the least, are rare.

The question of pulmonary malignancy resulting from repeated inhalation of irritating substances is brought up from time to time. Authorities on this subject dispute the possibility of irritation alone producing malignancy and state that it requires the activity of a specific carcinogen to produce such a condition. It would seem that if irritation alone were the important factor, pulmonary malignancies would have been noted much more frequently than they have in the past. The report on a high incidence of pulmonary cancer among chromate workers focused attention on this subject.[6] In this instance a specific carcinogen has not been identified and there was no correlation between evidence of upper respiratory irritation and the presence of pulmonary cancer. In chromate workers exposed to irritating fumes and dusts of chromates, chrome ulcers of the nasal septum develop with resulting perforations. It is stated in the conclusions of this report:

"The occurrence of nasal irritation and perforation does not necessarily imply exposure to kinds and quantities of chromium compounds capable of producing lung cancer."

The cases of lung cancer in chromate workers seemed to be limited almost entirely to a small group of workers in the industry where monochromates were handled. Here the exposure would seem to be to dust rather than to volatile substances. On the

other hand, evidence of local irritation was common in workers exposed to a wide variety of chrome compounds.

When a definite increase in lung cancer was noted a couple of decades ago, the increased use of tar and tar products was promptly suggested by some as the probable cause. This might seem to be a logical deduction in that tar does contain some carcinogenic substances. Still over the years it does not as yet seem to have been established that those working in tar are especially subject to lung cancer. The increase seems to have been quite general rather than predominantly in those exposed to tar or any other particular industrial material.

Prevention and Treatment

Prevention means avoidance of exposure to harmful concentration. This can be accomplished best by handling these materials in enclosed systems, and by ventilation. The latter is often satisfactory if prompt and adequate dilution is possible, but often means removal as near the source as possible by local exhaust ventilation. In circumstances where dangerous concentrations may be present personal respiratory protection may be required. Such equipment should not be depended upon in place of proper ventilation for regular exposures. In cases of emergency usually self-contained oxygen or compressed air equipment is indicated. When canister type gas masks are used these should be of a type approved by the U. S. Bureau of Mines for the particular substance and cannot be depended upon for any exposure of over 30 minutes or for over 2 per cent concentration in the air, or of course in an atmosphere of less than 16 per cent oxygen.

Treatment would call for prompt removal of the patient from the exposure and if breathing has stopped, the use of artificial respiration by either the prone-pressure, or Eve rocking method. With many irritants local treatment may be indicated. This would be symptomatic, usually by the use of emollient sprays, etc. When there is an exposure to a substance likely to produce edema of the lung, as for example oxides of nitrogen, oxygen therapy is indicated.[7] This should not be postponed until definite symptoms of edema appear. Used promptly and properly there is ample reason to believe that it can prevent the development of edema. The recommended procedure in these cases is as follows: Place patient at rest in bed. Administer 100 per cent oxygen, preferably exhaled against positive pressure of not more than 6 cm. (about $2\frac{3}{8}$ inches) of water. This can be arranged by connecting the face mask to a water bottle and inserting the tube not more than 6 cm. below the surface of the water. Administer 100 per cent oxygen in this way for 30 minutes out of every hour for

four to six hours. After this time treatment should be resumed should any symptom of respiratory distress appear.

SUMMARY

1) By far the greatest proportion of volatile substances have little or no direct action on the respiratory tract, even those which cause severe systemic effects when inhaled. For instance, ethyl alcohol, aliphatic and chlorinated hydrocarbones, carbon monoxide.

2) Many volatile substances have more or less superficial and transitory irritant effects with or without serious systemic action. Such as many of the ethers, esters and ketones.

3) Certain volatile substances do have marked irritating effects on the respiratory system, the symptoms varying principally with the area of the respiratory tract most affected. This area is largely determined by the solubility of the substance. Among these are ammonia, formaldehyde, sulphur dioxide, chlorine and oxides of nitrogen.

4) The effects produced by inhalation of volatile irritants are usually local and if not severe enough to be lethal, complete recovery generally follows without development of chronic or disabling changes.

5) Any conclusive evidence so far is lacking which would indicate that inhalation of volatile irritants predisposes to the development of chronic infections such as tuberculosis. Repeated inhalation of such irritants may however be a factor in the incidence of acute respiratory infections.

6) There is as yet insufficient evidence as to the part played by inhalation of volatile substances to demonstrate a causative relationship with malignant changes in the respiratory tract.

RESUMEN

1) La mayor parte de las substancias volátiles, aún las que causan graves efectos orgánicos cuando se inhalan, tienen muy poca o no tienen ninguna acción directa sobre el aparato respiratorio. Por ejemplo, el alcohol etílico, los hidrocarburos alifáticos y clorados, el monóxido de carbono.

2) Muchas substancias volátiles tienen efectos irritantes más o menos superficiales y transitorios, acompañados de una acción orgánica grave o sin ella, tales como muchos de los éteres, ésteres y ketonas.

3) Ciertas substancias volátiles sí tienen efectos irritantes marcados sobre el sistema respiratorio. Los síntomas varían principalmente de acuerdo con la zona más afectada del aparato respiratorio. Lo que más determina la zona afectada es la solubilidad de

la substancia. Algunas de estas substancias son: el amoniaco, el formaldehido, el anhidrido sulfuroso, el cloro y los óxidos de nitrógeno.

4) Los efectos producidos por la inhalación de irritantes volátiles generalmente son locales y, si no son lo suficiente graves para que sean letales, por lo general se obtiene una recuperación completa sin que se desarrollen alteraciones crónicas o que causen incapacidad.

5) Hasta ahora no se han aducido pruebas concluyentes que indiquen que la inhalación de irritantes volátiles predisponga al desarrollo de infecciones crónicas, tales como la tuberculosis. Sin embargo, la repetida inhalación de tales irritantes puede ser un factor en la incidencia de infecciones respiratorias agudas.

6) Todavía no hay suficientes pruebas del papel que desempeña la inhalación de substancias volátiles para demostrar alguna relación etiológica con las alteraciones malignas del aparato respiratorio.

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Cholesterol Pleural Effusion: A Report of Three Cases with a Cure by Decortication*

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Cholesterol thorax is one of the rare types of pleural effusion, some 60 cases having been reported in the literature. The pleural effusion is characterized by the presence of cholesterol crystals in the fluid, giving it a characteristic satin-like sheen when present in large amounts. This report deals with the study of three cases of cholesterol pleural effusion, each of which presents points of interest worthy of reporting. Case 1 is unique in that for the first time, pleural decortication was carried out with complete recovery after endless aspirations over a period of several years. Case 2 is of interest in that tubercle bacilli were found in the pleural fluid, a rare finding in cholesterol pleurisy. Case 3 presents an unusual cause of cholesterol effusion, a metastatic adenocarcinoma of the lung and pleura, the tumor producing mucin. This is the first time, so far as is known, that a cholesterol pleural effusion has been described, produced by malignancy.

Case Reports

Case 1. First Hospital Admission: B.T., a 44 year old white female entered Barnes Hospital on January 18, 1944. Her chief complaint was cough and slight pain in the left chest. She had a dry hacking cough for eight years. There was a weight loss of 12 pounds in the past two years.

Physical Examination: Temperature 37.5; pulse 72; respirations 18; blood pressure 140 82. Significant findings were in the chest. There was a marked lag on the left with dullness over the lateral half of the left chest anteriorly and posteriorly. Breath sounds were absent over this area. No rales were heard.

Laboratory Findings: RBC 3.44; Hgb. 11 gm.; WBC 8950 with a normal differential. Kahn test was negative. Tuberculin test was positive, second strength PPD. Roentgenogram of the chest showed a dense homogeneous opacity along the left lateral chest, obliterating the left costo-phrenic angle (Fig. 1). The lung fields were otherwise clear. The heart was pushed over to the right. Thoracentesis obtained 550 cc. of turbid yellow fluid which had a satin-like sheen. Specific gravity was 1.026. The fluid contained crystals of cholesterol, which when filtered off and washed with water gave the characteristic melting point. Analysis for cholesterol showed 2165 mgm. per cent concentration in the fluid. The fluid was

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practically acellular. No acid-fast bacilli were found on smear, culture or guinea-pig inoculation of the fluid. Sputum and gastric washings showed no acid-fast bacilli. Sedimentation rate was .7 mm min.

Course in Hospital: The chest was aspirated on three occasions averaging 300 cc. each time. She was discharged to the out-patient department on February 4, 1944.

Subsequent Course: While the patient was in the out-patient department, her thorax was aspirated on innumerable occasions, averaging about 350 cc. The fluid varied from the original yellow color to a reddish brown, but it always contained large numbers of cholesterol crystals. The last aspirations showed a lessening amount of cholesterol. She was readmitted to Barnes Hospital on May 27, 1947 for decortication of the lung, since it was obvious that the fluid would continue to reform.

Second Barnes Hospital Admission: May 27, 1947 to July 3, 1947. Physical examination revealed the same findings as on previous entry. Bronchoscopy was done on June 2, 1947. The carina was shifted to the left side. The mucosa of the left tracheo-bronchial tree showed a scarring and thickening but no acute inflammation. Slight stenosis of the left lower lobe bronchus was noted. The bronchoscopic picture strongly suggested old healed tuberculosis. The aspirated fluid showed a cholesterol value of 133 mgm. per cent. Total protein was 7.6 gms. per cent; albumen 4.6; globulin 3.

Operation, June 7, 1947: Decortication of the left lung was performed by Dr. Tom H. Burford. "The parietal pleura was greatly thickened. The lung was firmly bound down by a thick fibrinoplastic yellowish membrane which contained nodules of calcium and cholesterol deposits. The membrane was incised, a cleavage plane was begun by blunt dissection, and the membrane was stripped away from the upper and lower lobes of the lung. The dissection was carried peripherally and the reflection of the parietal pleura was also stripped from the thoraces of the chest wall, from the mediastinum and from the diaphragm. The entire thickened development of the peel was excised. Patient tolerated the procedure well."

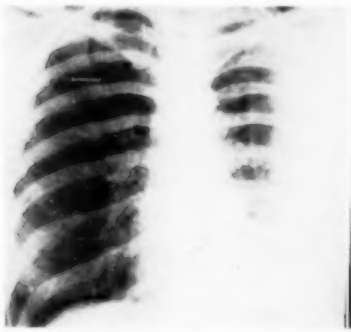

FIGURE 1

FIGURE 2

Figure 1, Case 1: Cholesterol effusion (December 20, 1943).

Figure 2, Case 1: Decortication of left lung. Fluid has disappeared (March 13, 1948).

Pathological Report: "The material consists of a fibrinous peel. It is 1 mm. in thickness, has a yellowish color with splotchy red areas. *Microscopic:* Sections of the membranous structure which is composed of very dense collagenous connective tissue with a very scanty nuclear component and a few blood vessels. There are a few round inflammatory cells infiltrating the various portions. There are no areas suggestive of tuberculosis. *Diagnosis:* Chronic Inflammation."

Later Course: The patient was discharged on July 3, 1947 and has been seen at monthly intervals since. There has been no return of the fluid (Fig. 2). Partial atelectasis of the left lower lobe remains, this being due in part to the original stenosis of the left lobe bronchus. The patient is at present asymptomatic as regards her chest.

Case 2: K.C., a white female, age 40, was first seen on May 24, 1948. She gave a history of having had tuberculosis about eight years previously, for which she received pneumothorax therapy up to 1944. This was discontinued at that time and she was discharged as arrested. Since 1944 she has been active as a housewife. Her chief complaint was frequent sore throats associated with joint pains.

Physical Examination: Temperature 37.4; pulse 74; respirations 18; blood pressure 120 80. Significant findings were in the chest. The right chest was dull particularly laterally and in the base. Breath and voice sounds were diminished. No rales could be heard.

Laboratory Findings: RBC 4.1; Hgb. 12 gms.; WBC 8000 with a normal differential. Roentgenogram of the chest showed a dense opacity along the lateral border of her right lung, obliterating the costo-phrenic angle (Fig. 3). There were numerous calcifications and fibrous-appearing nodules throughout her right lung. Her sputum was negative for tubercle bacilli.

Figure 3, Case 2: Cholesterol effusion containing tubercle bacilli.

Later Course: A diagnosis of pleural effusion was made. Aspiration was done on June 2, 1949 and 300 cc. of a slightly yellow turbid fluid was obtained with a characteristic satin-like sheen. Microscopically, numerous large cholesterol crystals could be seen. There were very few cells noted. A smear of the fluid showed M. Tuberculosis and a guinea-pig inoculated with pleural fluid developed tuberculosis during a five weeks period. Cholesterol content of the fluid was 900 mgm. per cent. Total protein was 8.3 gms. per cent; albumen 5.1; globulin 3.2. The chest was aspirated repeatedly up to May 1949. With each aspiration, fewer cholesterol crystals could be seen. She had a three day febrile period following each aspiration which then subsided. Tubercle bacilli could be repeatedly demonstrated in the aspiarted fluid. She was last seen on May 9, 1949.

Case 3: R.L.K., a 64 year old white male entered Barnes Hospital on April 8, 1949 with a chief complaint of shortness of breath for seven months. He had been a sander in a steel mill for the past two years. One year ago he noticed dyspnea on exertion. A chest film at that time was said to be negative. He then developed chronic cough with one cup of yellowish sputum daily. He worked until two weeks before admission, when dyspnea and weakness became so severe that he was completely incapacitated. He lost 30 pounds of weight in the past year. He had no chest pains, night sweats or fever.

Physical Examination: Temperature 37.2; pulse 76; respirations 18; blood pressure 130/85. Significant findings were in the chest. There was dullness to percussion in the right lower chest, anteriorly and posteriorly. Breath sounds were diminished.

Laboratory Findings: RBC 3.5; Hgb. 12 gms.; WBC 9000 with a normal differential. Kahn test was negative and tuberculin test was positive, second strength PPD. Roentgenogram of the chest showed a dense homogeneous shadow in the entire lower half of the right chest and a similar opacity along the upper mediastinal border, extending to the apex of the right lung (Figs. 4 and 5). Blood calcium was 9.3; phosphorus 2.2; alkaline phosphatase 2 B.U. Aspiration of the right pleural cavity on

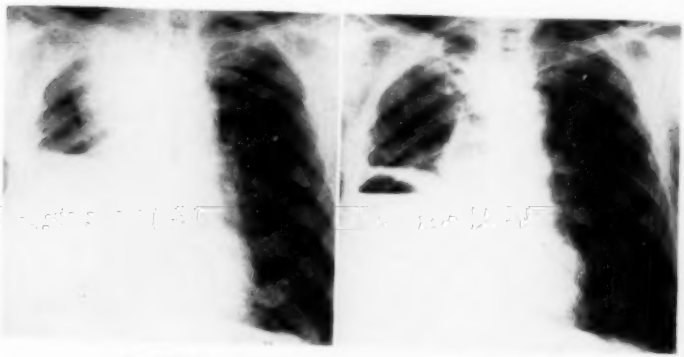

FIGURE 4

FIGURE 5

Figure 4, Case 3: Cholesterol effusion, associated with metastatic adenocarcinoma producing mucin.—*Figure 5, Case 3:* After aspiration, localized pleural and mediastinal effusion.

April 9, 1949 obtained 1150 cc. of a gray viscid fluid containing grossly visible cholesterol crystals. The cholesterol content was 170 mgm. per cent. The total protein of the fluid was 6.2 gms. per cent; albumen 4.5; globulin 1.7. The fluid was sterile and showed no acid-fast bacilli on smear or guinea-pig inoculation. Specific gravity was 1.032; cell count 150 cells cu.mm., all lymphocytes. A second aspiration was done on April 12, 1949 and 450 cc. fluid was removed. Specific gravity was 1.026; reaction 6.5. Total proteins of this specimen were 9.4 gms. per cent; albumen 4.5; globulin 4.9. Cholesterol was 83 mgm. per cent. Blood cholesterol on April 13, 1949 was 242.

Course in Hospital: Bronchoscopy done on April 14, 1949 was negative. Studies of the bronchial washings showed tumor cells present. He was referred to Chest Surgery and thoracotomy was performed on May 18, 1949 by Dr. Leonard Kemler.

Operative Findings: At operation, the pleura was found to be $\frac{1}{2}$ cm. thick. A free pleural space was found at the level of the 6th rib which contained 500 cc. of fluid resembling motor oil. There were many firm adhesions binding in the lower lobe to the parietal pleura. These felt like cartilage. The upper lobe was small and bound down by thick pleura and adhesions to the apex. Biopsy of the adhesions showed an adenocarcinoma. The tumor had invaded the lower lobe. Since the case was obviously inoperable, the chest was closed. Patient was discharged on June 16, 1949 and died shortly thereafter. No post-mortem was obtained. The final microscopic diagnosis was "metastatic adenocarcinoma of the lung, which is producing mucin. This could be metastatic from the large bowel" (Fig. 6).

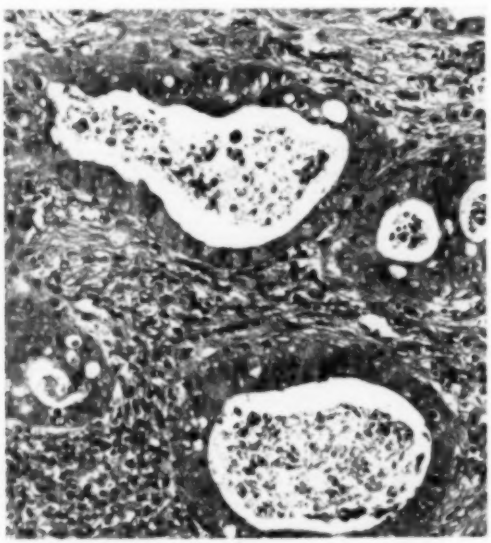

Figure 6, Case 3: Section showing metastatic pleural adenocarcinoma, which produces mucin.

Discussion

Cholesterol is practically always present in pleural effusions, being held in solution by some complex balance between the protein elements. When this balance is upset, cholesterol appears in the crystalline state and a so-called cholesterol effusion results. This is a chronic, recurrent encysted type of effusion, associated with a markedly thickened pleural membrane. It is usually found in the middle-aged, though one case has been reported in a nine year old boy who had previously had an empyema operation (Sharpe[1]). The effusion itself produces few symptoms. Slight cough, chest pain and a mild pyrexia may be present. Pressure phenomena due to the effusion are rarely noted except with large accumulations of fluid. Other symptoms that may be present are due to the underlying disease or to the development of some intercurrent disease.

The fluid itself is characteristic only insofar as it contains cholesterol crystals. With an appreciable amount, these can be readily seen grossly, often giving a satin-like sheen to the fluid. Microscopically, numerous large polyhedral colorless crystals of cholesterol are easily visualized. The fluid may be clear or turbid; varies from yellow through brown to red. The specific gravity is usually high. Microscopically, the sediment is practically acellular. The cholesterol content varies in amount, decreasing with repeated aspirations, but rarely if ever disappearing.

The etiology of cholesterol pleural effusion is not entirely clear. Tuberculosis, usually of an inactive type, is present in about half of the cases. Tubercle bacilli have rarely been found in the fluids, either on direct smear or by animal inoculation. Diabetes and syphilis have also been suggested as a cause. However, since tuberculosis is the most common cause of chronic pleural effusion, it is highly probable that it is the basis for most of the cases of cholesterous effusion. It is generally accepted that certain conditions are necessary for the precipitation of cholesterol crystals (Erwin[2]). First, there must be a persistent exudate containing cholesterol which is derived from the blood stream. Second, the pleura must be so thickened as to prevent normal interchange of constituents between the pleura and the circulating blood and lymphatics. This produces a delay in the process of resorption. Chronic, active or "healed" tuberculosis most frequently provides these conditions.

The source of the cholesterol in the exudate is under dispute. Barbiere and Tricaud[3] suggest that it comes directly from the blood, but in the majority of cases the blood cholesterol is normal. Desbordes and Levy, quoted from Erwin,[2] state that in long-

standing effusions, the total protein remains constant but an inversion occurs in the albumen globulin ratio. When this occurs, the cholesterolytic power of the fluid decreases and precipitation of cholesterol takes place. This has not held true for all cases as reported in the literature. Curran[4] states that some fluids on coming in contact with cholesterol tend to precipitate any cholesterol which they contain. Solid cholesterol from a degenerated or caseous focus in the pleura may cause such a change in the effusion. Once this has occurred, the process persists since some cholesterol crystals always remain after evacuation of the fluid.

Other theories as to etiology have recently been quoted by Lyons.[5] These include lipiodol degeneration of the pleura, destruction of the leucocytes in the pleural space, destruction of tubercle bacilli, and general metabolic disturbances. Cholesterol crystals have been found in the pericardial cavity (Alexander[6]). Tedeschi[7] and his associates recently reported a case of "pseudomyxoma peritonei" which originated from a previous pseudomucinous cystadenoma of the ovary and in which large deposits of cholesterol crystals were found in the exudate. Probstein and Lassar[8] noted cholesterol crystal inclusions in a case of appendiceal myxoglobulosis.

The three cases presented may now be reviewed in the light of the above-mentioned brief review of the literature. All of them have the necessary pre-requisites for the precipitation of cholesterol crystals. In each case, there was evidence of a thickened pleura and a long-standing encysted effusion. Case 1 had a pleural effusion of many years duration, in view of the infiltrations of the pleura with calcium and cholesterol. This patient probably had an old healed tuberculosis, though bacteriological confirmation was lacking. Clinically, she was relatively asymptomatic except for cough and chest pain. Her blood cholesterol was not increased. The A.G. ratio of the fluid was greater than one, thus discounting the theory of Desbordes and Levy. The cholesterol deposits in the pleura undoubtedly account for the constant new supply of cholesterol crystals in the effusion as noted over a three and a half year period of observation. For the first time, decortication of the pleura was done in a case of cholesterol thorax and the patient made a complete recovery. The operation was performed because of the necessity of repeated aspirations. In the presence of active pulmonary tuberculosis, decortication would be contraindicated. Also, in those cases in which the effusion might eventually disappear or is very small in amount, operation is not advised.

Case 2 is unusual in that tubercle bacilli were demonstrated on direct smear and by guinea-pig inoculation. The pleural effusion was present for approximately five years and followed artificial pneumothorax for pulmonary tuberculosis. Similar cases have been

described in the literature (Durham[9]). The appearance of the x-ray film would indicate the presence of calcifications and caseous lesions in the pleura and/or sub-pleural zone, and these are the probable sources of the cholesterol. The effusions in this patient showed an A.G. ratio greater than one. In view of the presence of tubercle bacilli in the fluid and the probably active lung lesion, decortication is not advised.

Case 3 is unique in that for the first time cholesterol pleural effusion is found associated with malignant invasion of the pleura. The tumor was described as a metastatic adenocarcinoma of the lung and pleura which was producing mucin and which probably arose from the large bowel. It is of considerable interest that in spite of the frequency of malignant effusions, precipitation of cholesterol crystals has not been previously described. It is true that in this case, the pleura was markedly thickened and the fluid was encysted so that the usual requirements for cholesterol effusion were present. Perhaps the reason that such an effusion is not seen more often in malignant pleurisies is because it is rare for the patient to survive long enough. The finding of a mucin-producing tumor in the pleura is of considerable interest and brings up the possibility of a relationship between mucin and cholesterol precipitation. Moreover, the pleural effusion in this patient was of less than a year's duration which is the shortest time on record for the appearance of cholesterol effusion. In this connection, the recent report of Tedeschi[7] and his associates of the association of a peritoneal mucinoid and cholesterol effusion in a case of pseudomyxoma peritonei may be of significance. Their case is reported as the first one of such a combination. Their explanation of the cholesterol precipitation is that the protracted exudation and thickening of the enclosing membranes produced the ideal conditions which caused "disruption of the albumin-globulin liason and resulted in precipitation of the cholesterol crystals." Does mucin have a tendency to precipitate out cholesterol from fluids or does mucin produce tissue changes which leads to an increased production of cholesterol? An attempt will be made to solve these questions in the laboratory.

SUMMARY

1) Three new cases of cholesterol pleural effusion are reported.

2) Complete decortication of the pleura in a patient with cholesterol thorax was done for the first time and resulted in a clinical cure.

3) Cholesterol deposits in the pleura in one case and caseo-calcific pleural deposits in a second case were responsible for the

high cholesterol content of the fluid and the precipitation of cholesterol crystals.

4) The first case of cholesterol pleural effusion associated with adenocarcinoma of the pleura is described. The tumor was a mucin-producing tumor and brings up the possibility of a connection between mucin production and cholesterol precipitation.

RESUMEN

1) Se informa sobre tres nuevos casos de derrames pleurales colesteáricos.

2) Por la primera vez se llevó a cabo una decorticación completa de la pleura en un paciente con colesterotórax, y ello resultó en una curación clínica.

3) Depósitos de colesterina en la pleura, en un caso, y depósitos pleurales caseocalcíficos, en uno otro, fueron la causa de la elevada concentración de colesterina en el derrame y de la precipitación de cristales de colesterina.

4) Se describe el primer caso de derrame pleural colesteárico asociado con adenocarcinoma de la pleura. Fue éste un tumor que produjo moco, lo que sugiere la posibilidad de que exista alguna conexión entre la producción de moco y la precipitación de colesterina.

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Pericardiotomy for a Shifting Bullet

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This man of 22 years, was admitted to the Hong Kong Sanatorium and Hospital on September 27, 1948, for bullet wound in the chest.

History of Injury: On September 12, 1948, while out for a walk, he was suddenly wounded by a stray bullet discharged during a fight between two rival gangs of gamblers. The gun was fired about 50 yards away, and killed one man outright about five feet away, then the bullet penetrated the patients right chest. In the excitement, he ran for a few minutes until he discovered blood trickling from his side. He was treated at a hospital in Canton, China, for one week.

On admission to the Hong Kong Sanatorium and Hospital, there was a small wound on the right mid-axillary line. The temperature was normal and there was no leucocytosis. The principal complaint was pain on inspiration.

X-Ray Inspection: The bullet entered the right chest at a point where the mid-axillary line crosses the sixth rib. It had apparently penetrated further than the pleura and the right lung.

The antero-posterior radiograph taken in Canton following the injury showed that the bullet was then lodged at a point where the left border of the sternum crosses the third anterior intercostal space.

Our radiographs taken 15 days later indicated that after the bullet had travelled from its entry across the chest for seven inches horizontally, it had descended downwards and to the left for another three and one-half inches—a total course of ten and one-half inches and was finally lodged in the vicinity of the apex of the heart.

As a final check-up before the day of the second operation, the bullet's antero-posterior position was marked fluoroscopically by a metal button and when the x-ray was taken with the patient lying on his left side, to our surprise the position of the bullet was found shifted to the left and cephalward one and one-fourth inches!

First Operation: October 1, 1948. Two inches each of the sixth rib and its cartilage were resected to the sternum using a six inch

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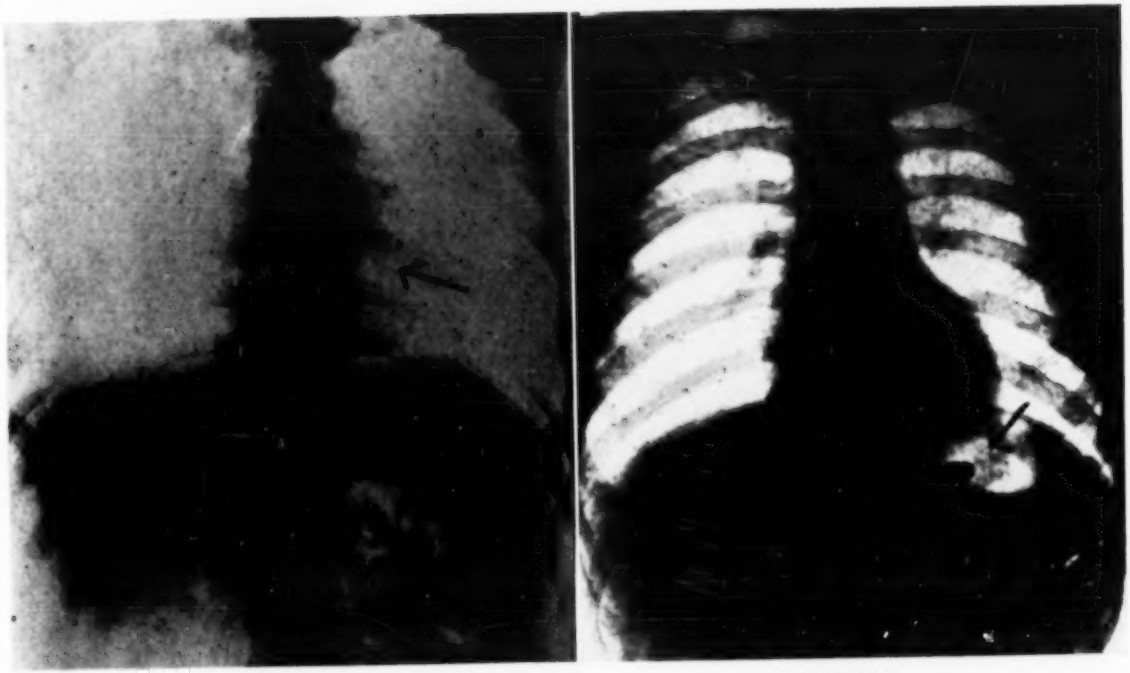

FIGURE A FIGURE B

Figure A: Radiograph (antero-posterior) taken on admission to the hospital in Canton showing the original position of the bullet at the junction of the 8th posterior intercostal space and the left border of the spine.—*Figure B*: Radiograph taken on admission to the Hong Kong Sanatorium and Hospital showing the final position of the bullet approximately 1¼ inches to the left of the left border of the spine, having descended to the level corresponding to the upper border of the 11th rib posteriorly.

curved incision with its convexity towards the left. The parietal pleura was opened vertically for four inches and the chest was explored for about one hour without result. The pericardium was not opened for exploration due to the patient's weakening condition even though he was receiving 500 cc. of human plasma plus one litre of dextrose saline given intravenously. The wound was closed air tight in layers. Convalescence was speedy and uneventful and the wound healed by first intention.

Second Operation: October 23, 1948 (22 days later). Under endotracheal anaesthesia and intravenous plasma, the scar of the first operation was excised and the wound reopened and extended upwards for another two inches. This time, a bigger chest window was made by an additional resection of the rib and one and one-half inches each of this rib and its cartilage were resected to the sternum. The old scar tissue was largely excised and the chest cavity reopened.

After the left lung was collapsed on the entry of air, the chest was again systematically explored, but no bullet was palpable. As a last resort, the pericardium was opened vertically through its left antero-lateral border for one and three-fourths inches. To our surprise, there was no gush of fluid which the x-ray suggested, as the pericardial shadow was much increased. However, the exploring finger broke through numerous adhesions.

After a lengthy search, a slippery hard lump suggestive of the bullet was discovered just below the heart's apex. It was then hooked up by the finger and pressed against the chest wall to fix it for dissection.

The hardened tissue was incised under direct vision until the glistening of the nickel-coated bullet flashed across the opening. To extract it with forceps was straightforward enough provided the benumbed finger hooking it would not let it slip away again.

The wound was drained and closed in layers. Before it was completely closed, the lungs were inflated with positive pressure and a solution of warm penicillin poured into the pericardial and chest cavities. The pericardium was closed by a continuous chromic catgut. Recovery was uneventful and he was discharged on November 17, 1948, 25 days after the second operation.

Comment

1) The patient was singularly fortunate in escaping injury to the important left lung hilus structures as well as the heart itself, as it happened to be a hard-nosed bullet.

Apparently, the missile penetrated the right side of the pericardium just anterior to the myocardium, having lodged there

for a while and then gravitated within the pericardium to a level below the heart's apex through locomotion.

2) The pre-operative radiographs indicated shifting of the bullet according to the patient's position. In order to afford a more valuable guide to the surgeon, it is suggested that radiographs should be taken strictly according to the direction of the proposed surgical approach when special locating instruments are unavailable.

3) The enlarged radiographic shadow of the heart is undoubtedly due to the thickened pericardium arising from pericarditis.

4) The fact that the wound was practically free from infection is ascribable to the heated missile.

5) While the calibre of the bullet is somewhat small (7.63 mm.) for a lethal weapon, the mauser-pistol of this type has a surprising range of 1,000 meters. The cartridges are loaded with smokeless ballistite. Hence the same bullet after having killed a man 50 yards away was still powerful enough to penetrate seven inches across the patient's chest. That he was able to run for a few minutes after having been hit indicated that despite its terrific range, the small solid bullet was incapable of delivering a knock-out blow.

Naturally a soft nose missile would be more destructive by virtue of its mushrooming expansion following impact, in which case it would probably be fatal.

6) In all intra-thoracic operations endotracheal anaesthesia is now the method of choice whereby positive pressure can be used to inflate the lungs.

The Non-Cooperative Patient

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Two questions come to mind whenever one discusses the problem of the non-cooperative patient, first: Is the management of such a patient an important item in general tuberculosis control? and second: Is a compulsory hospitalization law necessary?

Tuberculosis is a contagious disease. The most important single method of prevention is the isolation of the infectious individual from contacts. This isolation can be accomplished by confinement in the sanatorium or the same results obtained by exercising proper precautions in the home away from the sanatorium.

When open cases of tuberculosis are permitted to roam the community at will doing such things as attending theatres, movies and athletic contests, promiscuous shopping in stores, mingling with crowds, riding in public conveyances, and living in the same house with children, then an ample supply of fresh cases will always be assured—and the Superintendents of Tuberculosis Hospitals will never have to worry about unemployment.

In the past the most fruitful source of pulmonary tuberculosis was the unknown case. With the continuation of community wide x-ray surveys and other case-finding methods, the unknown case promises to dwindle in importance and then the guilt will rest almost solely on that small group of non-cooperatives.

In the city and county of Peoria during 1948 it was found that there was an average of 124 known contagious cases of pulmonary tuberculosis. Seventy seven of these or 62 per cent were isolated in hospitals. The remaining were out of the hospital. Of these, 20 were confined in their homes under supervision following prescribed precautions. Twenty-seven, or 21 per cent were out of the hospital, either in their homes, or roaming the streets refusing to cooperate and using few or no precautions toward spreading their disease to others. It is this small residual of patients that will certainly account for the majority of new cases.

In Columbus, Ohio a study was made of 150 non-cooperative patients with pulmonary tuberculosis. The results were published in the Ohio State Medical Journal for May 1942. All these patients had a fair to good chance of getting well when the diagnosis was

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made, and the treatment they refused, whether it was bed rest, sanatorium care, or surgery, was thought at that time to be an important factor in anticipated recovery. The condition of these patients at the time the paper was published was as follows: 6.6 per cent well or improved; 7.3 per cent quiescent; 86 per cent worse, hopeless, or dead.

The reasons for refusal were given as follows: Felt well, 64 per cent; going to others for treatment, 38 per cent; sex maladjustment, 22 per cent; family doctor did not encourage, 20 per cent; long sanatorium waiting list, 14 per cent; fear of sanatorium, 10 per cent; misunderstood, 10 per cent; did not believe diagnosis, 10 per cent; sanatorium overcrowded, 8 per cent; loss of income, 8 per cent; liquor, 6 per cent; too much free care, 6 per cent; religious prejudice, 5 per cent.

The most significant part of this study was that 134 of these cases were asked at a later date, when they were aware that they had made a mistake, what they thought could have influenced them to submit to treatment. Seventy-four per cent said that nothing short of legal force could have influenced them. Other reasons given in their order of importance were: more health information, more attractive surroundings in sanatoria; less waiting for entrance to sanatoria; closer cooperation by private physicians, and adequate provisions for dependents.

Under authority of a compulsory hospitalization law passed by the Ohio Legislature in 1943, the Benjamin Franklin Tuberculosis Hospital at Columbus has established a separate section for recalcitrant patients. Information supplied by Gerald Fry, Executive Secretary of the Columbus Tuberculosis Society reveals that there has been little difficulty in the administration of the isolation unit. The support of public opinion had been attained by radio

CHART I

STAGE OF THE DISEASE

	Number	Per cent
Minimal	5	6.7
Moderately advanced	11	14.8
Far advanced	58	78.4

Number of Months Non-Cooperative

Shortest	1 month
Longest	100 months
Average	29.4 months
Total Number of Months	2,173.5

65,205 Man Days of Contagibility

and newspaper education prior to the opening of the unit. In the regular hospital the number of discharges against medical advice has dropped from 33 per cent before the unit opened, to 18 per cent afterwards, and is still dropping. Enforced isolation is reserved for the worse violators—those who refuse to follow prescribed public health regulations and decline to enter the sanatorium through regular channels.

We have compiled at Peoria a list of 74 patients residing either in the city of Peoria or in the County outside of the city who can definitely be considered a menace because of their refusal to follow prescribed precautions. To be on this list each patient must be highly contagious as evidenced by a persistent positive sputum, and the degree of non-cooperation must be such as to leave no doubt that the individual is a danger to others. Some portion of the observation period in these 74 cases occurred between the years 1946 and 1950.

The number of months these patients were considered non-cooperatives averaged 29.4 per patient (Chart I). The shortest period was one month, the longest 100 months. Fifty-eight, or 78 per cent were far advanced, 11 or 15 per cent were moderately advanced, and five or 7 per cent were considered minimal.

Forty-nine were females and 25 were males (Chart II). When compared to all new cases of tuberculosis in Peoria during the past five years, the non-cooperative group showed no significant

CHART II

SEX

	All Cases Tuberc. (1945-1949)		Non-Cooperative	
	Number	Per cent	Number	Per cent
Male	321	64.4	49	66.2
Female	177	35.6	25	33.8
	498		74	

AGES

	All Cases Tuberc. (1945-1949)		Non-Cooperative	
	Number	Per cent	Number	Per cent
Under 15	5	1.0	1	1.3
16-25	77	15.5	16	21.6
26-35	114	22.9	17	22.9
36-45	100	20.1	19	25.6
Over 45	202	40.5	21	28.4
	498		74	

sex difference. Considering ages, the non-cooperatives as a whole were younger than all cases diagnosed. This could partly be accounted for by the desire to build a career and the necessity of supporting a family in the young and middle aged.

Chart III shows the manner of non-cooperation. Eighty-nine per cent refused to follow any instructions whatsoever in their homes. The fact that children were in the home was not in itself considered a violation of instructions, unless there was no attempt to isolate the children from the contagious case.

The reasons as interpreted by Clinic Physicians and Tuberculosis Nurses after careful analysis of each case are given in Chart IV. Each patient presented an individual problem. Most of them had several reasons that contributed to failure to achieve cooperation.

The insidiousness of tuberculosis means that even those with advanced disease may *feel well*. This was important in creating

CHART III

MANNER OF NON-COOPERATION

	Number	Per cent
No precautions in home	66	89.2
Rides public transportation	55	74.3
Breaks clinic appointments	51	69
Promiscuous shopping	39	52.8
Children in home	38	51.3
Eats and drinks in restaurants	31	41.9
Working with public	22	29.7
Attends public gatherings	21	28.4

CHART IV

REASONS

	Number	Per cent
Inadequate	35	47.3
Feel well	25	33.8
Alcohol	17	22.9
Refuses to believe diagnosis	15	20.3
Desire to treat self	10	13.4
Financial	8	10.8
Marital difficulties	5	6.7
Fear of family break-up	5	6.7
Homesickness	5	6.7
Want to change climate	4	5.4
Pressure of family	4	5.4
Fear of surgery	4	5.4
Religion	4	5.4
Sex maladjustment	3	4.0
Stigma	2	2.7

poor cooperation and was felt to be a definite factor in a third of these patients. *Alcohol* affects the person two ways: causing him to leave the hospital against advice to get a drink and by continuous drunkenness, the individual has neither the will nor the time for any other activity. *Refusing to believe diagnosis* is a defense mechanism whereby the patient solves his problem simply by not believing. The *desire to treat self, homesickness, want to change climate,* and *fear of surgery* are frequently only excuses and not real reasons. Inadequate *financial* resources is often a great stumbling block toward proper care and this condition can seldom be remedied by public relief agencies. *Marital*

CHART V

INADEQUATE

Below average mentally	6
Psychotic	4
Domineering, spoiled, selfish, used to getting own way	12
Nervous, weak willed, unstable	6
Shiftless, never gets along, can't hold jobs, accomplishes nothing	5
Antisocial, mean	1
Criminal	1
	35

Alcohol was a contributor in	8
Prostitution in	2
Spent some time in Mental Institutions	7

CHART VI

SUGGESTED REMEDIES

Legal Measures		60
Breakdown:		
Prevent working		1
Threat to remove child	(2)	2
Removal of children by court		2
Quarantine	(1)	3
Threat of hospitalization	(1)	5
Enforced hospitalization	(1)	33
Mental institutions	(6)	14

( ) parenthesis = measure was tried and was successful.

Social work		9
Take pensions away	(2)	4
Financial help for dependents		1
		74

difficulties, fear of family break up and *sex maladjustment* are serious obstacles. The *pressure of family* and close associates frequently causes the patient to leave the sanatorium or to resume normal activities too early. *Religion* played a part in four of these patients. Again this may only be an excuse to get out of doing something unpleasant. *Stigma* means that the person will stay away from tuberculosis agencies and hospitals because he doesn't want his friends to know he has the disease.

Thirty-five or 47.3 per cent were considered to be *inadequate*. By this we mean that they had a mild to severe inability to adjust themselves to sanatorium life. Thirty-four of these left a sanatorium against medical advice. Of these, 25 were readmitted for a second try and 21 left the second time against advice. The other four were very ill having attained the terminal stage of their disease and this acute illness or early death may have prevented them from leaving again. Inadequacy was demonstrated by the many instances of multiple leave against advice in these patients. One young man had the known record of leaving against medical advice 13 times.

Chart V attempts to classify these inadequates according to their type of personality. We realize that this attempt is not only inaccurate, but with apologies to the psychiatrist, presumptious. Expense and time involved meant that very few of these people had the benefits of psychiatric consultation. It is interesting to note that since tuberculosis is no respecter of persons or character, that one of these cases actually had a long criminal record, eight were chronic alcoholics, prostitution played a part in two, and seven of the 35 had spent some time in mental institutions.

In a careful review of all these case histories by the physicians of both the County and City Chest Clinics, by the Public Health

CHART VII

EFFECT OF REHABILITATION

	Total No. Discharged	No. Discharged A.M.A.	Per cent
1944	184	65	35.3
1945	110	40	37
1946	117	44	37.6
1947*	87	17	19.5
1948	92	16	17.4
1949	100	19	19

*In Sanatorium Rehabilitation Program Started April 1947.

Nurses and the rehabilitation co-ordinator, including in many cases personal interviews, several remedies are suggested (Chart VI).

Discussion

Some of the blame for the existence of the non-cooperative patient in any area must be attributed to the physicians, nurses, and other tuberculosis workers who are conducting the tuberculosis control program for that community. There are many things that can be done to cut down on the number of recalcitrant patients short of legal force.

Public health education is important in gaining public and individual cooperation. This education carried on in the schools, magazines, newspapers, on the radio, and individual instruction by nurses, doctors, and organizations should keep emphasizing such things as: tuberculosis is contagious—symptoms of this treacherous disease are frequently absent or mild—and tuberculosis is curable. Health education is most effective if administered before the diagnosis.

Social work is invaluable in straightening out misunderstandings, in education of family and friends, in getting evidence for anticipated court procedures, in pointing out those individuals needing psychiatric help, and in correlating the resources of all available agencies, especially in regard to securing financial help for dependents.

All too frequently the involved patient is ineligible for relief and for aid to dependent children, and if he is eligible, the funds supplied are often much less than his needs. Getting on relief means stripping the family of its resources and savings, and some patients are just not willing to do this. One answer of course would be health and accident insurance, but adequate health insurance is expensive and all but a few are unwilling to carry it. Pensions for the tuberculous wage earner as long as he is under treatment might be of value. One measure that has been successful in Peoria is for the rehabilitation co-ordinator to secure part time or home work for dependents of a patient under treatment. The Peoria Production Shop which offers graduated sheltered work for those convalescing from tuberculosis has recently given employment on a part or full time basis to dependents of patients.

Rehabilitation not only in the Sanatorium but after the patient leaves should be an important factor in cutting down un-cooperativeness. A patient learning a new trade or taking a refresher course will frequently prolong the treatment period because he is not so apt to think he is wasting his time.

The Peoria Municipal Tuberculosis Sanitarium started an exten-

sive In-San Rehabilitation Program April 1, 1947. Practically 100 per cent of all patients participate in this program and over 30 per cent actually take some form of vocational training. Chart VII shows the leave against medical advice was much higher before this program was started *than afterwards*. Of course, other factors may have influenced this but we believe that rehabilitation definitely helps keep the patient in the sanatorium.

Making the sanatorium more attractive is another *must* measure. This includes: an adequate number of private rooms for the very ill, keeping the transfers and moves to a minimum, frequent redecorating, beautifying the grounds, movies, entertainment, good food, and a helpful attitude toward the patients by the medical and nursing staffs.

When the patient leaves the sanatorium with permission, to stay in his home, frequent medical check-up examinations and supervisory visits by the public health nurse will help to keep him in line.

Legal measures include many things short of enforced hospitalization, such as denying employment to patients with contagious tuberculosis, making transportation companies liable for knowingly transporting contagious tuberculosis patients without permission from the Health Department, removal of children from the infected home by court action, threat of quarantine, actual quarantine and threat of enforced hospitalization.

Quarantine in the home is often difficult to carry out and sometimes is impossible. It may mean constant employment of police supervision. When the patient lives in a boarding house or hotel or is simply a transient going from place to place, quarantine is impossible.

If enforced hospitalization becomes necessary, then there are several methods that have been and can be employed, depending on the individual case and state and local laws:

1) A sentence in the local jail or workhouse for quarantine violation. The disadvantage of this method is the difficulty in getting jailers to accept contagious cases, and the fact that the imprisoned patient is not likely to get any treatment for his tuberculosis.

2) Commuted sentences to the workhouse or jail, and parole of the patient to the superintendent of the local sanatorium with the understanding that if he leaves the sanatorium against advice he is required to serve his sentence.

3) Building separate sections complete with bars and locks in local or centrally located sanatoria where enforced isolation can be carried out.

4) Giving a definite sentence to these quarantine violators,

placing them in a prison tuberculosis hospital already located within the confines of the prison, or in a prison hospital located near the State tuberculosis sanatorium. This, of course, would mean the mixture of the non-cooperative patients with other prisoners who have tuberculosis.

If enforced hospitalization is used, then a provision should usually be made for the transfer out of incarceration to regular sanatorium facilities whenever the patient signs a statement promising cooperation.

CONCLUSIONS

1) Legal proceedings which include both quarantine and enforced hospitalization should best not be used until there are ample treatment facilities in the community for *all*.

2) All other means should be used before actual force is employed and this includes threat of force.

3) Laws must be specific and detailed and evidence of contagibility and non-cooperation must be overwhelming.

4) Regulations must be impartially enforced.

5) Enforced confinement should be reserved for the most flagrant violators.

6) The problems of the patient must be kept foremost in mind—leniency must be practiced whenever possible.

SUMMARY

1) Management of the non-cooperative patient is an important tuberculosis control measure.

2) It appears that successful management can never be completely attained without the aid of a compulsory hospitalization law.

CONCLUSIONES

1) Es mejor que no se empleen procedimientos legales, que incluyen la cuarentena y la hospitalización forzosa, sino cuando ya existan amplias facilidades en la comunidad para el tratamiento de *todos*.

2) Deben agotarse todas las otras medidas antes de emplear la fuerza o la amenaza de fuerza.

3) Las leyes deben ser especificas y detalladas y las pruebas de la contagiosidad y de la falta de cooperación deben ser abrumadoras.

4) Se deben hacer cumplir imparcialmente los reglamentos.

5) Debe reservarse el encierro forzoso para los violadores más flagrantes de la ley.

6) Los problemas del paciente deben recibir debida consideración y se debe aplicar la ley con lenidad, siempre que sea posible.

RESUMEN

1) El manejo del enfermo que no coopera es una medida importante en el control de la tuberculosis.

2) Parece que no es posible resolver satisfactoriamente este problema sino con la ayuda de una ley de hospitalización forzosa.

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The Epidemiologist and Eradication of Tuberculosis

H. A. BURNS, M.D., F.C.C.P.*
Anoka, Minnesota

Tuberculosis has been recognized as a dangerous contagious disease for a long time, and was proved to be such nearly 70 years ago, when Robert Koch (1882) discovered the tubercle bacillus.

Even though we have an abundance of information concerning the contagious character of this infection, our concept of the epidemiology of tuberculosis is still burdened by controversies. Because of this uncertainty in our understanding of the biology and epidemiology of tuberculosis, we are often inclined to assume that both Koch's discovery and his law must be accepted in general, but with reservations when tuberculosis as an entity in the gallery of parasites is in any way concerned.

During a long period of time since man began to congregate in larger and more permanent groups, tuberculosis has become more firmly entrenched as a powerful and determining factor in the affairs of men. Time and opportunity have given the germ the privilege of spreading itself throughout the world. It has successfully adjusted itself to man's social and economic development to the end that it has brought prosperity to itself locally and spread geographically throughout much of the later years of man's history. Even now we often find ourselves helpless in defending our own bodies against the threat of their becoming unwilling hosts to this minute and apparently helpless germ. Once infected, we wait with uncertainty and indecision, possibly even alarm, as to what plan may froce the germ to assme the role of a harmless parasite.

The germ causing tuberculosis cannot live and multiply in nature separated from man and his domestic animals. So, also, once gaining access to their bodies, it cannot survive by becoming and remaining benign. The germs may seem inactive at times under certain conditions, but this is more apparent than real and given an opportunity, they can and often do demonstrate their virulence and their ability to kill. Survival for tubercle bacillus must depend upon countless generations by fission in human and animal bodies. Even this alone will not be assurance that the germ will live. There must be established a relationship between the germ and

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the body cells that make the development of tubercles possible. These tubercles once developed must undergo a series of changes characteristic of the disease. This tiny parasite is taken up by some of the cells in the body which in turn are destroyed by bacilli. The collection of germs and cellular tissue, both living and dead, become a tubercle and serve as a headquarters for the activity of the invading organism. Such small tubercles joining together may form one or more larger tubercles. The central part eventually becomes filled with tissue cells that have been destroyed as a result of their contact with the invading germ, pus and caseation resulting.

As the relationship between parasite and host continues, the location of the tubercle in relationship to the blood, lymphatic supply, and the air passages becomes of more and more importance. By the use of the lymph flow and the blood facilities, rapid distribution to distant parts even to other organs may occur within a short period of time. Proximity to air passages may save the tubercle bacillus the necessity of developing its own sinus tracks since it will have an opportunity to use the respiratory track as a means of getting its discharges from the source of origin to the outside world.

The future of the tubercle bacillus depends almost wholly upon its ability to find a way of escape to the outside and to establish almost immediate contact with a person or animal. The changes occurring in the body converting a simple infection into one of great epidemiological significance may graphically be shown as follows:

While for purposes of classification the progression of the disease known as tuberculosis begins somewhere between C and H (Fig. 1), it is unfortunate that from an epidemiological point of view the disease is still usually reported piece meal. G is usually reported, but not often in the earlier groupings. These forms of tuberculosis are made known to the health officer much oftener than all the others, yet they are less dramatic and less dangerous than the pulmonary forms of the disease.

G, I, K, N, O, Q, and R, all of which may be duplications, are now usually reportable. All the remaining key positions in the pattern of the disease remain unrecognized. The epidemiologist is seldom brought into the tuberculosis problem before G or I is reached. Prior to this period, biological survival is not possible for the tubercle bacillus.

When should the tubercle bacillus be recognized as a disease-causing germ? When does it warrant the concern of the epidemiologist and at just what stage should it be considered reportable?

We know that stages A and B are the beginnings of tuberculosis.

Moreover, we know that consumption cannot evolve without the disease passing through these stages. *Unfortunately these or none of the later stages result in the development of dependable immunity in people or animals.* There may be one or several small accumulations of cells close together or at some distance in stages A and B. These are called endothelial cells and are always closely associated with tubercle bacilli. The cells in growing have the habit of grouping themselves well rounded within and becoming flat towards the outside even to the point of forming a capsule about the outside of the nodule. While blood cells and giant cells frequent the nodule, there is no evidence of irritation or inflammation surrounding the development of the nodular growth.

C. The period of early allergy may begin sooner than two months following the first development of tubercle. The so-called "State of Allergy" is recognized soon after infection and remains to re-

Schematic Plan of Tuberculous Disease

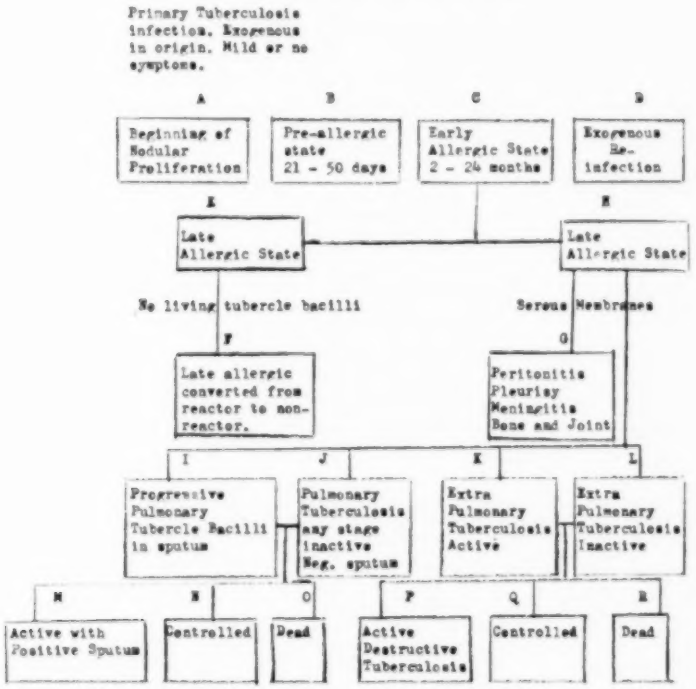

Fig. 1

spond to the presence of tubercle bacilli so long as they remain alive in the body. As soon as the cells have become allergic to the protein of the germ, the behavior pattern of the invading infection becomes recognized as a specific infection. The nodular growth of cells is the first response of the body to the invader.

The beginning of the second phase ends the first after a few days or weeks at most. This second phase is characterized by the development of allergy. With the tissue cells of the body being hypersensitive, allergy becomes a most important factor in the development of tuberculosis. Inflammation now comes to be an important aid in the continued evolution of the tuberculous infection from its pre-allergic state to consumption. With inflammation, there may also occur toxemia, suppuration, active tissue destruction, and infection of the serous membranes resulting in meningitis, pleurisy, pericarditis, peritonitis, synovitis and extensive blood stream infection.

While tubercle at A and B is essentially proliferative, stage C is an exudative "irritation reaction." We understand the structural changes going on by the simple procedure of the tuberculin test. We now know that the body has reacted anatomically during the few days when the germ first entered the body by the growth of small nodules in the vicinity of the germs. With allergy, we have also a series of changes that would not have occurred to any great extent, if at all, except for allergy. With the germ reacting to this condition, multiplying and extending to new areas even to distant parts as a result of this state of general hypersensitiveness. E to O and R are the usual sequence in the development of tuberculosis.

It is strange that a parasite so dangerous to us can live in our bodies short, by weeks only, of its dramatic ending without our being able to notice any change in our sense of well-being. It is strange too that man and his tubercle at both ends of the scale of development show an uncanny similarity in their ability to adjust themselves to a complicated pattern of existence and still survive.

The time element varies between phases from a period involving months to one of years. *We are frequently permitted to think that our early association with the tubercle bacillus is a beneficial one. It often does not result in immediate or startling consequences; however, there are many cases each year giving mute testimony to the fallacy of this sort of thinking.*

With the extension of tubercle and its resulting fibrosis, proliferation, and necrosis with possible cavity formation, the disease tends to become chronic over a variable period of time depending upon the anatomical relationships with neighboring tissue and the nearness to its food supply. These conditions, as well as the number

of dividing organisms (fission) in the new implantation, determines each step in the further extension of the disease, in any particular area. It is this phase of tuberculosis that indicates the tubercle bacillus to have developed in man a superior type of the carrier state. No other germ has perfected man to be so satisfactory a carrier as is the case in tuberculosis.

Many sanatoria have been provided to care for and isolate these carrier cases. Educational programs have been a universal aid to acquaint the carrier and his associates as to the safe relationships to be maintained in order to protect the uninfected. Much of our treasure and our energy has been expended in an effort to apologize for and to plan to live comfortably and with relative safety with tuberculosis. *We should accept no condition except its complete eradication.*

A study of tuberculosis was made in one family known to have had an older member who had been an open case for many years during which time he frequently visited relatives. This experience occurred in an American Indian family that had separated into two groups prior to the time when the carrier case had become a danger to others. One group left the reservation and moved to industrial centers completely separating themselves from their earlier influences and never having contact with the members of the family who continued living on the reservation.

Group I consists of 93 members who live on the reservation. Group II is composed of 105 members who have separated themselves from the reservation and the relationships that had previously been a part of their reservation life.

In Group I where exposure became rather constant at times over a period of years, the family had 23 members who died of tuberculosis. During the same period there was one death in Group II. At the time this study was made there were 13 members of this family belonging in Group I who were known to be suffering from some form of active tuberculosis, while there was no known case among the members of Group II.

Tuberculosis has received considerable attention throughout the years as a contagious disease with an heredity background. It is evident from this family group that if there was any tendency for tuberculosis to pick out certain individuals because of an heredity predisposition to tuberculosis that the disease should have been about as prevelent in the group that left the reservation as it was amongst those that continued to live on in the old way. Time and experience does not lend force to the argument that there is any such influence transmitted from the parent to the child.

The development of tuberculous disease may depend somewhat

upon the dosage that is able to establish itself in the original invasion. Their ability to live and multiply (fission) is an important factor. Implantations of the parasite into humane tissue must depend on the accumulation of dosage, partially through fission and also through large numbers of the germ being introduced with repetitions over a period of time.

When enough tubercle bacilli become localized, the problem may be one of months and possibly years of growth and development under adverse conditions before the organism is in a position to involve sufficient tissue to endanger the well being of the host. It may be a much longer time before there has been adequate necrosis to make the escape of organisms from the host possible. Once such escape occurs, it may continue over a period of months or for many years. The carrier state once established frequently remains as a permanent relationship between the parasite and its host.

The repeated contact of family members with the uninfected permits intimate exposure repeated at more frequent intervals than would be the case in most instances of exposure. Breaking up such contacts in the family through the providing of isolation beds has been one of the major factors in blocking the transfer of large doses of organisms and hence has resulted in the lessening of the incidence of tuberculous infection and the clinical breakdown of those infected.

The time element is always important in the epidemiological study of disease. It is as characteristic of tuberculous infection as it is in the development of other parasites which invade our bodies.

During the onset of measles, typhoid fever, diphtheria, or scarlet fever, the infection falls into a uniform pattern within a few days at most, and the struggle between tissue cell and parasite is both severe and of short duration. The diagnosis of the type of disease can usually be told depending upon exposure and the onset of prodromal and later clinical and laboratory findings. We know under ordinary conditions just how the average case of measles or typhoid fever will behave. We know that in measles it requires 14 days for the organism to extend from a focal to a general infection. With typhoid fever, the incubation period, ending in prodromal symptoms, usually requires from two to three weeks before clinical typhoid fever becomes recognized. We know that within a period of less than six weeks the tissue cells have either successfully combated the disease or the patient has died, or that through localizing in some organ or area, the organism has become a local infection permitting the host to survive as a carrier.

In the little town of B a heavy storm backed up the sewage in a pump pit from which the community was supplied with its drink-

ing water. There was a demonstrated leak in the sewage connection which overflowed the pump thus contaminating the city water supply. This condition lasted but a few days. Within two weeks many citizens became ill with an acute gastrointestinal infection. Within three weeks cases of typhoid fever began to appear, and within the next few days there were 106 people sick with this disease. In this community, by the prompt use of control methods, cases resulting from contact with these primary water-born cases were limited to 12. The germ causing typhoid, in order to survive, must follow a pattern for such survival between epidemics.

This is true with many germ-born diseases, and search will disclose the fact that the parasite has often retreated in the body to become established in a small area or organ still preserving its virulence and its threat of danger. It may be an infected sinus draining from a lymph node or a localized infection in a bone, or it may be a chronic infection of the gall- bladder. In scarlet fever, it may be the lymph nodes or an infected mastoid or middle ear. With diphtheria virulent germs may hibernate in a small symptomless ulcer in the posterior nasal region. Any of these may be the source of further infected foor supplies or contact cases over a long period of time. It is the development of these residual carrier states that the germ depends upon for survival rather than the high incidence of infections commonly seen in epidemics.

In many of these communicable diseases, we have limited the spread to the carrier and an occasional individual contact. Vaccines, toxins, and the protection of our food and water supplies have all done much to limit these infections to relatively small areas. By lengthening the time interval between epidemics we will eventually eliminate the infection en masse which actually explains the origin of the "Carrier State." Time alone, by making the development of carriers impossible, can completely eliminate these infections as a danger to our lives and health.

In the little village of M, the dairy that supplied most of the milk in the town was run by a careful and clean family. They took every precaution they knew to give their patrons a supply of clean raw milk. The milker, of course, did not know that the cause of a slight sore throat might find a satisfactory home in his milk. He did not know then that a child ill in the house would develop a rash in another day, and within a week there would be over 100 cases of scarlet fever in the village quite definitely traced to his sore throat and his milk supply. After the epidemic there were the carriers still in the village or moving in many directions aiding to keep scarlet fever a potential threat against the life and well-being of the children over a large area of countryside and nearby villages.

The tubercle bacillus does not live its existence in so dramatic a manner nor does it depend on quite the same simple carrier state that is commonly seen in other contagious diseases. It has developed and accommodated itself to man in such a way that the experience must be one of ancient origin. It has so far accepted man and domestic animals as its normal hosts that it is no longer able to exist in nature outside of their bodies. It has been able to stand in man's way socially and culturally devitalizing his finances and his body, yet, using him as a carrier and the food supply for its own propagation and prosperity. It has so impressed the mind of man that few have ever planned on the elimination of tuberculosis but rather on its control. It has forced man to play the role of an apologist when he should be out as a gladiator. In no other infectious disease have we an organism so dependent upon us for its existence or are we given so much time in which to plan our defense against the invader.

After the tubercle bacillus invasion first occurs, the problem of the epidemiologist is one presenting many complexities involving our social, economic, and cultural existence as well as the use of our medical and scientific knowledge.

Many communicable diseases have now been reduced to what may be considered irreducible minimums. This is true in large areas of the world population, and family groups, depending upon the type of parasite involved. Surely we have gone far in our handling of plague, cholera, hydrophobia, and dysentry. Community infections like typhoid fever in many large areas of the world no longer remain a serious danger. The same applies to smallpox, diphtheria, scarlet fever, and enteritis of infancy; yet, we do not completely destroy the organism as a biological parasite. There seems to be a final retreat from which, under favorable conditions, they emerge to renew their attack. We seem to recognize some inherent right of the organism to continue to live at times and under certain conditions that we recognize as an endemic reappearance of the organism.

In tuberculosis, the epidemiologist has the same experience with variations that have been gone over in the past with other forms of parasites. We must pursue the retreat of the tubercle bacillus far beyond any accepted standard of irreducible minimum to complete biological disappearance.

SUMMARY

1) Tuberculosis was proved to be a dangerous contagious disease when the tubercle bacillus was discovered nearly 70 years ago.

2) This organism is dependent upon multiplication in human and animal bodies for survival.

3) The stages through which tuberculous lesions must evolve before the disease decomes contagious are shown schematically.

4) Failure to detect the disease in people and animals during the first few months of its existence often leads to first reporting cases after bacilli are being disseminated to human and animal associates of hosts.

5) Dependable immunity does not develop from the presence of virulent tubercle bacilli in any stage of the lesions they produce. Therefore, humans and animals with tuberculous lesions do not become immune so as to prevent exogenous or endogenous reinfections.

6) We must no longer be satisfied with measures intended only to control tuberculosis. Eradication is the goal of the epidemiologist.

RESUMEN

1) Con el descubrimiento del bacilo tuberculoso, hacen casi 70 años, se comprobó que la tuberculosis es una enfermedad contagiosa y peligrosa.

2) Para sobrevivir, este microbio necesita multiplicarse en los cuerpos de seres humanos y de animales.

3) Se demuestran esquemáticamente los periodos que deben atravesar las lesiones tuberculosas antes de que la enfermedad se vuelva contagiosa.

4) La falta de descubrir la enfermedad en personas y animales durante los primeros meses de su existencia a menudo conduce a que no se comuniquen los casos sino después de que los bacilos se hayan difundido a seres humanos y a animales que han estado en contacto con los huéspedes.

5) La presencia de bacilos tuberculosos virulentos no resulta en el desarrollo de una inmunidad segura en ningún periodo de las lesiones causadas por los bacilos. Por consiguiente, los seres humanos y los animales con lesiones tuberculosas no adquieren una inmunidad que evite las reinffecciones exógenas y endógenas.

6) Ya no debemos estar satisfechos con medidas que sólo traten de controlar la tuberculosis. La erradicación de la enfermedad es el objeto del epidemiólogo.

Editorial

THE COMMON COLD

The common cold and its sequelae constitute the great incapacitators of American citizenry. Among children and young adults, 23 per cent have as many as four or five colds annually and only 17 per cent have only one cold or none each year. An attack of the common cold usually incapacitates for only three or four days, but there is always the possibility of complications which may result in prolonged ill health and even death. For example, the paranasal sinuses may become involved with resulting chronic sinusitis. This, in turn, may be followed by subacute and chronic bronchitis. Not infrequently pneumonia appears upon the heels of the common cold, which may result in serious complications such as bronchiectasis and pulmonary abscess. Otitis media is another complication, sometimes leading to mastoiditis. More time is lost from school by children in the grades and young adults in high schools, colleges and universities from colds than from any other disease.

Among elderly persons the common cold is a serious threat in itself and not infrequently leads to killing conditions such as pneumonia.

Between childhood and old age, including the decades of greatest productivity of humans, the common cold is a constant and serious menace to health. It has been estimated that among the 60,000,000 presently employed persons in this country, each one is absent from two to three days on the average annually because of colds. Thus, 180,000,000 work days are lost. If the average income of workers were $6.00 per day, the total yearly wage loss would be $1,080,000,000. This does not include loss in production, suffering and mental anguish or contagiousness of workers' disease to members of their families and other associates.

Among the 60,000,000 workers of this country, there is much worry resulting in inefficiency when serious colds and their complications attack and incapacitate members of their families.

When the common cold with all of its ramifications is considered among the approximately 150,000,000 people of this country, its cost is staggering.

Numerous attempts have been made to devise methods of preventing the common cold such as the employment of vaccines, but nothing has yet been found to materially reduce the onslaught of this disease.

A large variety of medicinal preparations have been used and some of them alleviate symptoms. The most recent and exten-

sively employed are the antihistamine chemicals. Soon after they were introduced for this purpose, about 1947, like so many other preparations of the past, their value was widely acclaimed. However, more recent scientific studies and observations have dampened enthusiasm for them. Results of such studies appeared in the September, 1950 issue of *Industrial Medicine and Surgery*. The article by W. L. Baughn is there summarized, as follows: "In 18 months, constituting three six-month cold seasons in the past 27 months, 8079 colds have been treated with 43,000 doses of antihistamine medication of seven different brands. In addition, 2131 colds have been treated with control medication. Antihistamine subjects numbered 4627, and 1336 controls reported and have been used in this analysis. Popular response to the medication was good, an average of 66 per cent feeling they had achieved perfect results in 48 hours. The control group felt they had derived 27 per cent perfect results. Side reactions were reported by an average of 23 per cent of the test group. Severe reactions were rare and transient.

"Two rational hypotheses were set up to prove the worth of the drugs in reducing the incidence of fully developed colds and time lost to the plant due to colds, and were treated by objective evidence from personnel records and by a random cross-section poll, without revealing any evidence of the therapeutic efficacy which had been hoped for. It is felt, however, that the drugs provide excellent symptomatic relief for colds at the cost of some risk of side reactions, and that by careful selection of dose and interval this risk can be made comparable to that run with other standard cold medications."

Another article by Frank R. Ferlaino carries the following summary: "Numerous investigators have reported that much benefit can be derived from the use of antihistaminic drugs in the treatment of the symptoms of the common cold. The antihistamines are not a cure-all. The body defense mechanism still plays an important role in curing the true virus common cold.

"1. The indiscriminate use of antihistaminic drugs among workers in industry is to be avoided because of possible side effects. It has been a practice of industrial physicians to remove the worker from dangerous machinery while he is taking antihistaminic drugs.

"2. It is advisable to give workers who operate intricate machines a trial therapy period with an antihistaminic drug while off the job, to determine in advance whether there are any undesirable side reactions, such as drowsiness. With the experience gained and with proper instructions from the industrial physician, workers will know in advance whether they can use these new antihistaminic agents with safety while at work.

"3. Not all antihistamines cause exactly the same reactions.

Therefore, it is a matter of selecting the most effective drug for the individual which will cause the fewest side reactions.

"4. All available statistical studies and other scientific data indicate that the antihistaminic drugs have a legitimate place in the treatment of the symptoms of the common cold. Among workers, their effectiveness is limited by the unfavorable side reactions which occur. The specific cure for the common cold, whether it be an antibiotic agent, a sulfa drug or a vaccine, is still to be discovered."

At the request of the Ministry of Health, the British Medical Research Council arranged for an extensive series of tests which were conducted on 1550 cold sufferers. The special committee of the Medical Research Council who carried out these tests reported that, "The drugs had little if any value in either the prevention or treatment of the common cold."

While some workers have found the antihistamine chemicals of limited value when carefully prescribed, it is obvious that to date these drugs do not afford the solution of the common cold problem. Obviously extensive research on all phases of the common cold is imperative. The expenditure of vast sums of money to promote the research work of a large number of scientists and clinicians is necessary in order that theories may be tested and facts assembled which may lead to the control of this scourge of humanity. It is encouraging that such a research program is being planned by the American Research and Education Foundation for Chest Disease.

J.A.M.

College Chapter News

FIRST INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

The First International Congress on Diseases of the Chest held in Rome, Italy, September 17-22, 1950 was attended by nearly one thousand persons including doctors, wives and friends from forty countries. Many of the doctors who attended are just returning home after a post-convention tour of Europe. A selected group of the scientific papers and a more detailed report of the Congress, including photographs, will be published in future issues of "Diseases of the Chest."

EUROPEAN CHAPTER ORGANIZED

A European Chapter of the College was organized following the Rome Congress. Dr. Andre Meyer, Paris, was named secretary of the chapter. The executive committee of the chapter will be comprised of the Regents and Governors of the College in the European countries. It is planned to hold the first meeting of the European Chapter in Paris in 1951 and subsequent annual meetings will be held in various European countries.

ITALIAN CHAPTER PLANNED

An Italian Chapter of the College, with 104 members, will be organized at Naples in April of 1951. The chapter will meet jointly with the Italian Federation Against Tuberculosis and present a program on non-tuberculous diseases of the chest. Officers for the chapter will be selected at this meeting.

FRENCH CHAPTER ORGANIZED

A French Chapter of the College has been organized with four new Governors in addition to Professor Paul Veran of Nantes. The new Governors are: Dr. Andre Meyer and Dr. Maurice Bariety for Paris, Dr. Paul Santy for Lyon and Dr. F. Piechaud for Bordeaux. Professor Etienne Bernard is the Regent for France. Dr. Andre Meyer, secretary of the European Chapter, will also serve as secretary-treasurer of the French Chapter.

The following committees have been appointed:

Committee on Surgery: Dr. Paul Santy and Dr. Olivier Monod.
Committee on Bronchology: Dr. Jean M. Lemoine and Dr. Andre Soulas.
Committee on Biology: Dr. Jacques A. DeLarue and Dr. Gernez Rieux.

ISRAEL CHAPTER ORGANIZED

The organizational meeting of the Israel Chapter of the College was held in Tel-Aviv on Wednesday, August 23, 1950. The following officers were elected for the ensuing year:

Pinchas Wayl, M.D., Jerusalem, President
Hugo Adler, M.D., Raanana, President-Elect
Kurt Friedmann, M.D., Tel-Aviv - Jaffa, Vice-President
Juda M. Pauzner, M.D., Tel-Aviv - Jaffa, Vice-President
Maurizio Mendes, M.D., Raanana, Vice-President
Otto Lichtwitz, M.D., Haifa, Treasurer
Chaja Brynberg, M.D., Tel-Aviv - Jaffa, Secretary.

Dr. Juda M. Pauzner was appointed Governor of the College for Israel.

FIFTH ANNUAL POSTGRADUATE COURSE IN DISEASES OF THE CHEST.
AMERICAN COLLEGE OF CHEST PHYSICIANS, OCTOBER 16-20, 1950, ST. CLAIR HOTEL, CHICAGO, ILLINOIS

Some of the physicians and instructors who participated in the Fifth Annual Postgraduate Course in Diseases of the Chest of the American College of Chest Physicians.

THIRD ANNUAL MEETING, CENTRAL BRAZILIAN CHAPTER

Hospital S. Sebastiao, Rio de Janeiro, August 7, 1950

Speakers platform (top picture), reading from left to right: Dagmar Choves, M.D., Helio Fraga, M.D., Gama Lobo, M.D., Flavio Fraga, M.D., Affonso MacDowell, M.D. (Regent of the College for Brazil), Ugo Pinheiro Guimaraes, M.D. (Vice-President, Central Brazilian Chapter), J. M. Castello Branco, M.D. (Treasurer, Central Brazilian Chapter), Reginaldo Fernandes, M.D. (Governor of the College for Central Brazil), Affonso MacDowell Filho, M.D. (Secretary, Central Brazilian Chapter).

College News Notes

Sir Alexander Fleming, London, England, was appointed Regent of the College for Great Britain and Professor Eugenio Morelli, Rome, was appointed Regent for Italy.

Dr. Alton Ochsner, New Orleans, Louisiana, Governor of the College for Louisiana, was named President-Elect of the American College of Surgeons at their annual meeting held in Boston, October 23-27, 1950.

Dr. Paul H. Holinger, Chicago, Illinois, was recently appointed Professor of Bronchoesophagology at the University of Illinois College of Medicine.

Dr. Enrique Iturbide, Guatemala City, Guatemala, was awarded a Gold Medal for his work in tuberculosis by the Republic of Honduras.

Dr. Carl H. Gellenthien, Valmora, New Mexico, was elected Vice-President of the American Association of Railway Surgeons at its recent annual meeting.

Dr. A. H. Baker, Calgary, Alberta, Canada, has recently retired from both the directorship of the Division of Tuberculosis Control and the superintendency of the Central Alberta Sanatorium.

The antibiotic laboratories of Hektoen Institute for Medical Research of Cook County Hospital has been named for the late Dr. Italo F. Volini of Chicago who died on June 24, 1950. Dr. Volini, who was a Regent of the College at the time of his death, was one of the Institute's founders, a member of its board of trustees and a pioneer in antibiotic therapy.

Dr. José Rosenberg of Sao Paulo, Brazil, has been appointed Governor of the College for South Brazil.

POSTGRADUATE COURSES

There were fifty-one physicians registered for the Fifth Annual Postgraduate Course in Diseases of the Chest which was presented in Chicago during the week of October 16-20. A photograph of some of the physicians and instructors who participated in the course appears in this issue of "Diseases of the Chest." The Third Annual Postgraduate Course in Diseases of the Chest presented in New York City during the week of November 13-17, had a registration of ninety-six physicians.

The Cuban Chapter of the College will present a postgraduate course in diseases of the chest during the week of December 18-22, 1950. The course is to be presented at the Instituto de Cirugia Ortopedica in Havana.

A postgraduate course in diseases of the chest will be presented at Vanderbilt University, Nashville, Tennessee, during the week of January 22-27, 1951. The course is sponsored by the American College of Chest Physicians, Southern Chapter, in cooperation with the Vanderbilt University School of Medicine. Tuition fee for the course is $50.00 and applications are now being accepted. For additional information please turn to advertising page viii in this issue of "Diseases of the Chest."

During the week of February 13-17, 1951, a postgraduate course in diseases of the chest will be presented at San Francisco, California, under the sponsorship of the California Chapter, American College of Chest Physicians, in cooperation with the University of California Medical School and Stanford University School of Medicine.

FOURTH URUGUAYAN CONGRESS ON TUBERCULOSIS

The Fourth Uruguayan Congress on Tuberculosis will be held in Montevideo on December 11 and 12, 1950 under the presidency of Dr. Fernando D. Gomez who is Regent of the College for Uruguay.

Obituaries

Italo Frederick Volini

ITALO FREDERICK VOLINI

1893 - 1950

Dr. Italo Frederick Volini was born on May 24, 1893 in Chicago, Illinois, the son of Dr. Camillo and Virginia (Botto) Volini. He was educated at the University of Chicago, B.S. 1915; and Rush Medical College, M.D. 1917. In 1925 he married Marcella Ringwald. Dr. Volini served as Professor of Medicine at Cook County Graduate School of Medicine, of which he was vice president and member of the Board of Trustees and chairman of the Department of Medicine. He was Professor and Head of the Department of Medicine, Stritch School of Medicine of Loyola University since 1929, and a member of the President's Council of Loyola University. Dr. Volini also served as vice president and attending physician of Cook County Hospital and as consultant to Holy Cross, Columbus, Oak Park, St. Anne's, St. Bernard's, St. Elizabeth's Hospitals and St. Mary's Hospital, Gary, Indiana. He was honorary president of the staff at Mother Cabrini Hospital and Columbus Hospital, and a staff member of the department of medicine at Grant Hospital, St. Joseph's Hospital, University Hospital and Frank Cuneo Hospital; Professor of Medicine, Chicago College of Dental Surgery, Loyola University; Board of Directors, Provident Hospital Associates; Board of Directors and Treasurer, member Public Relations Committee, American Research and Education Foundation for Chest Disease; Executive Board Hektoen Research Institute. Dr. Volini was former Dean of the Stritch School of Medicine of Loyola University.

Dr. Volini was active on the Executive Board of the Catholic Charities, a Knight of Saint Gregory and a member of the Knights of Columbus Chicago Council. He was a member of the Medical and Surgical Society of Bologna, Italy, and the Academy of Medicine of Rome, Italy. He was a member of the III Inter-American Cardiological Congress and was official delegate for the Italian Government appointed by the Italian Premier to the A.M.A. Centennial, Atlantic City, New Jersey in 1948. Dr. Volini served on the board of governors of the Chicago Heart Association and the Illinois Heart Association and was a member of the scientific council of the American Heart Association.

Dr. Volini was a Fellow of the American Medical Association and the American College of Physicians, former president of the Chicago Society of Internal Medicine, member of the Illinois State Medical Society, Chicago Medical Society, Mississippi Valley Medical Association, Asso-

ciation for the Study of Internal Secretions, Chicago Society of Medical History, Institute of Medicine of Chicago and the Central Society of Clinical Research. He was a member of the Board of Trustees and medical advisor of the Hematology Research Foundation; Founder and member of the United States Committee in support of the World Medical Association; member of the national executive committee of American Medical Relief for Italy; Chief Associate Examiner, National Board of Medical Examiners; Fellow, American Association for the Advancement of Science; member, American Board of Internal Medicine, subspecialty Board of Cardiology, Chicago Tuberculosis Society, Medical Advisory Council of Cook County Institutions.

He was a former director of the Italian Chamber of Commerce and former president of the Italian Academy of Medicine and the Dante Alighieri Society. He had also served as chairman of the Board of Directors of the Banco di Napoli Trust Company. Dr. Volini had received two decorations: Italian Government Cavaliere and Cavaliere Officials of the Crown of Italy.

During the First World War he served as lieutenant, U. S. Army A. E. F. He was a former member of the Board of Education of Chicago.

Dr. Volini was a Fellow of the American College of Chest Physicians, held office as Governor of the College for the State of Illinois, and at the time of his death was Regent of the College for District No. 7. He also served as secretary and member of the Council on European Affairs of the College.

More than 63 articles on Dr. Volini's investigations in clinical research have been published. He died on June 24, 1950 and is survived by his widow and ten children.

Charles K. Petter, M.D., Governor for Illinois.

KARL SCHAFFLE

1883 - 1950

Dr. Karl Schaffle was born in 1883. He received his degree of Doctor of Medicine from the University of Pennsylvania School of Medicine in 1907.

Dr. Schaffle served as consultant in medicine to the Highland and Memorial Mission Hospitals, Asheville, and was a member of the consultant staff of the Western North Carolina Tuberculosis Sanatorium, Black Mountain, North Carolina. He also served as editor of the Buncombe County Medical Society Bulletin and the Veterans Administration Bulletin. He was a Major in the U. S. Public Health Reserve Corps.

Dr. Schaffle was one of the pioneers in the tuberculosis movement in Asheville. He was associated for a number of years with the late Dr. Charles DeWitt Colby who directed the William Le Roy Dunn Memorial Clinic in Asheville, North Carolina.

For a number of years Dr. Schaffle served as Governor of the American College of Chest Physicians and at the time of his death, he was serving the College as Regent for District No. 5. His interest in College activities was well appreciated and he shall be long remembered by his many friends and colleagues.

Dr. Schaffle was a Diplomate of the Board of Internal Medicine and a Fellow of the American Medical Association.

George C. Crump, M.D., Governor for North Carolina.

UBALDO E. ZAMBARANO

1899 - 1950

"The good deeds of men, surviving them often unheralded and unsung, are far nobler memorials than those contrived by man." This is true of Dr. Ubaldo E. Zambarano, a good physician, friend, and counselor to countless numbers, who died in the Rhode Island Hospital on May 29, 1950.

He was born in Providence June 29, 1899. He received his early education in Providence and graduated from the Georgetown University Medical School in 1924. He served his internship at the Gallinger Municipal Hospital, Washington, D. C. and was resident physician at the Detroit Municipal Tuberculosis Hospital from 1925 to 1928. In 1929, he returned to Providence to become assistant to Dr. John I. Pinckney at the Providence Tuberculosis League where he remained until appointed superintendent of the Rhode Island State Sanatorium at Wallum Lake, July 15, 1939. On January 1, 1949, he became Executive Secretary and Medical Director of the Providence Tuberculosis League filling the vacancy due to the death of Dr. John I. Pinckney.

He was a member of the Rhode Island Medical Society and Providence Medical Association becoming the President of the latter on January 1, 1950. He served actively in many national organizations. He was former Governor of the Rhode Island Chapter of the American College of Chest Physicians; former President of the New England Group of the American College of Chest Physicians; an organizer and former Treasurer of the New England Tuberculosis Rehabilitation Society and former Director at large with the National Tuberculosis Association and former instructor of clinical medicine at the University of Vermont. Locally he was active in many organizations. He was a member and former President of the Providence Malpighi Medical Society; member of the executive committee of the Rhode Island Tuberculosis and Health Association. He served on the consulting staff of the following hospitals: Rhode Island, Roger Williams General, Charles V. Chapin, Pawtucket Memorial and Providence Veterans, also the Rhode Island State Sanatorium and the Belmont Hospital, Worcester, Massachusetts.

He has been heard over the air in the series "Doctor's Orders." He had tuberculosis pamphlets translated into different languages: French, Italian, Polish and Spanish.

He started the first pneumothorax clinic at the Charles V. Chapin Hospital and as Chief of the State Tuberculosis Control organized pneumothorax clinics in Bristol County, Cranston and Westerly. His work as Superintendent of the State Sanatorium was outstanding. Under his direction, Chest Surgery increased by leaps and bounds.

He was a fine administrator, an excellent doctor, but above and beyond all else he reached the heights in sympathetic guidance of the individual. This last trait bore fruit times without number when patients, determined to leave the hospital against advice, after a talk with "Dr. Zam," would reconsider and remain. We could go on and on but his work is too well known to require further comment. He devoted his best years to this cause and died with a task unfinished, a great loss to those agencies concerned with the control of tuberculosis.

His vision of an all inclusive program for the future is well known too and appreciated by his many associates in this work. With these

great achievements to his credit "Zam," as he was affectionately called by all, was unpretentious, kindly and friendly to everyone. His versatility, wit, and humor was the delight of his friends. His hobbies, photography and music, often served a dual purpose. Entire clinic procedures have been directed and filmed by him. It has been said in some cases where medicine was no longer of any avail, his music had soothed and made tranquil the final journey of a patient. Never was he too busy to give this individual attention. Countless numbers have left his office comforted and sustained by his sympathetic understanding of their problems.

Perhaps the most generally observed and appreciated side of his nature was his cheerful friendliness, which encompassed all. This trait was no specious counterfeit, no "professional manner." His interest in others was sincere and far-reaching. It was heart-wrenching for his friends when they went to see him in what we knew were his last days. He showed no concern for himself; his whole interest was centered on his friends and their families. It is an unusual being who maintains his cheerfulness and gusto while he is waiting for an inevitable finality.

It is seldom granted us the good fortune to know such a rare personality and "Zam" will always have a warm place in our hearts. His memory should serve as a beacon light for those left to carry on the work for which he so ably gave his all.

Of him we can truly say:

"For dearly must we prize thee, we who find
In thee, a bulwark for the cause of men." — William Wadsworth.

Edward Alfred Greco, M.D.
Frank A. Merlino, M.D.
Richard H. Overholt, M.D.

STEWART SEIBERT SHAFFER

1892 - 1950

Dr. Stewart Seibert Shaffer was born at Chambersburg, Franklin County, Pennsylvania on October 5, 1892, the son of John Wesley and Martha Adaline Shaffer. He graduated from the University of Maryland, School of Medicine in 1919 and served an internship at the Bay View Hospital (now Baltimore City Hospitals). Early in his medical career he became interested in diseases of the chest. He did research work on fungus infection of the lungs and then became interested in pulmonary tuberculosis. His work at the Maryland State Sanatorium began in 1921. In 1940 he became superintendent of Mount Wilson Branch of the Maryland Tuberculosis Sanatorium, where he remained until his death from hypertensive cardiovascular disease January 28, 1950 at the age of fifty-seven.

Dr. Shaffer, though intensely interested in clinical medicine and teaching, found time to carry on other activities. In his younger days he sang bass with a glee club and remained a lover of symphony music throughout his life. He served on the Frederick County Council of the Boy Scouts of America. His hobbies were photography, cabinet work and

radio. At one time he was Second Vice-President of the Frederick County Medical Society. He was a member of the American Medical Association, the Medical and Chirurgical Faculty of the State of Maryland, the American College of Chest Physicians and the American Trudeau Society.

Otto C. Brantigan, M.D., Governor for Maryland.

ANTHONY B. DANISAWICH

1897 - 1949

Dr. Anthony B. Danisawich was born in Mahanoy City, Pennsylvania on July 24, 1897. He was a graduate of Jefferson Medical College of Philadelphia in the class of 1922. He engaged in postgraduate studies in surgery at the University of Pennsylvania during 1924-1925 and was engaged in the private practice of medicine and surgery from 1925 to 1930. Dr. Danisawich served as staff physician at the Hamburg State Sanatorium from 1931 to 1939, at White Haven Hospital from 1939 to 1940, and at Mont Alto State Sanatorium, South Mountain, Pennsylvania from 1940 to 1948. While at Mont Alto State Sanatorium he served as chief of surgery and during several months of 1947 as acting medical director. Dr. Danisawich was hospitalized at St. Mary's Hospital, Rochester, Minnesota when he passed away.

Burgess Gordon, M.D., Governor for Pennsylvania.

COLLEGE EVENTS

17th Annual Meeting, American College of Chest Physicians, Atlantic City, New Jersey, June 7-10, 1951.

Semi-Annual Meeting, Board of Regents, Cleveland, Ohio, December 3 and 4, 1950.

Cuban Postgraduate Course, Havana, Cuba, December 18-22, 1950.

Southern Postgraduate Course, Nashville, Tennessee, January 22-27, 1951.

San Francisco Postgraduate Course, San Francisco, California, February 19-23, 1951.

Philadelphia Postgraduate Course, Philadelphia, Pennsylvania, March 26-30, 1951.

MEDICAL SERVICE BUREAU

POSITIONS AVAILABLE

Chief Resident Physician and Assistant Medical Director for J.C.R.S. Sanatorium, Spivak, Colorado. Salary commensurate with experience, plus full maintenance. Apply to Medical Director.

Senior Resident Physician wanted for a modern two hundred and forty bed New Jersey Tuberculosis Sanatorium. An American graduate with adequate training in a modern tuberculosis sanatorium. Experience in selecting surgical tuberculosis cases and with postoperative care is required. Civil Service examination not required. We do not have a State income tax. Doctor with wife and one child acceptable. Complete maintenance on the grounds granted. Salary open. Give complete information in first letter. Address all inquiries to Box 247B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Full time house physician, Lutheran Sanatorium, Wheat Ridge, Colo. Unfurnished house available. Salary commensurate with training. Apply to Medical Director.

Physician wanted for residency in tuberculosis sanatorium. One fourth of all admissions nontuberculous. Surgery done by diplomate of American Board of Thoracic Surgeons. Active Out-patient service. Contact Superintendent, Hopemont Sanatorium, Hopemont, West Virginia.

Position as Assistant Physician available January 1st; 100-bed county sanatorium, California resort area. Excellent opportunity for training chest surgery. Starting salary $400 per month plus furnished house and family maintenance. Apply to Medical Director and Superintendent, Ahwahnee Sanatorium, Ahwahnee, California.

POSITIONS WANTED

Associate or partnership in chest work. Experienced chest specialist. Willing to make investment. Now holding responsible position. American and graduate of Class A medical school. Excellent references. Please address all inquiries to Box 245B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

Diplomate of the American Board of Surgery and Fellow of the American College of Surgeons seeks permanent position as thoracic surgeon in a sanatorium. Will locate anywhere, preferably west coast. Address all inquiries to Dr. Thomas F. Keyes, 166 Dove Street, Rochester, New York.

British physician, married, 37 years old, seeks position in a sanatorium or chest department of hospital. Excellent references from Brompton Hospital, Paddington Chest Clinic and St. Charles Hospital. Needs definite assurance of position before visa will be issued. Address all inquiries to Box 246B, American College of Chest Physicians, 500 North Dearborn Street, Chicago 10, Illinois.

BINDING FOR COMPLETED VOLUMES

We are pleased to announce that The Book Shop Bindery, 308 West Randolph Street, Chicago, Illinois, will produce a well-bound volume at as low a price as possible for those members and subscribers who wish to preserve their issues of DISEASES OF THE CHEST. They will bind the six issues of Volume XVIII in the best grade of washable buckram with gold stamping on the spine and the member's or subscriber's name in gold on the front cover. Please send the six issues to Chicago by express or parcel post prepaid with check or money order for $3.15 made payable to The Book Shop Bindery. The bound volumes will be returned with transportation prepaid by the bindery.

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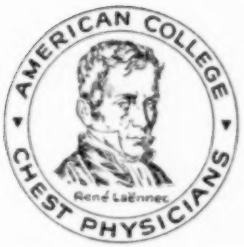

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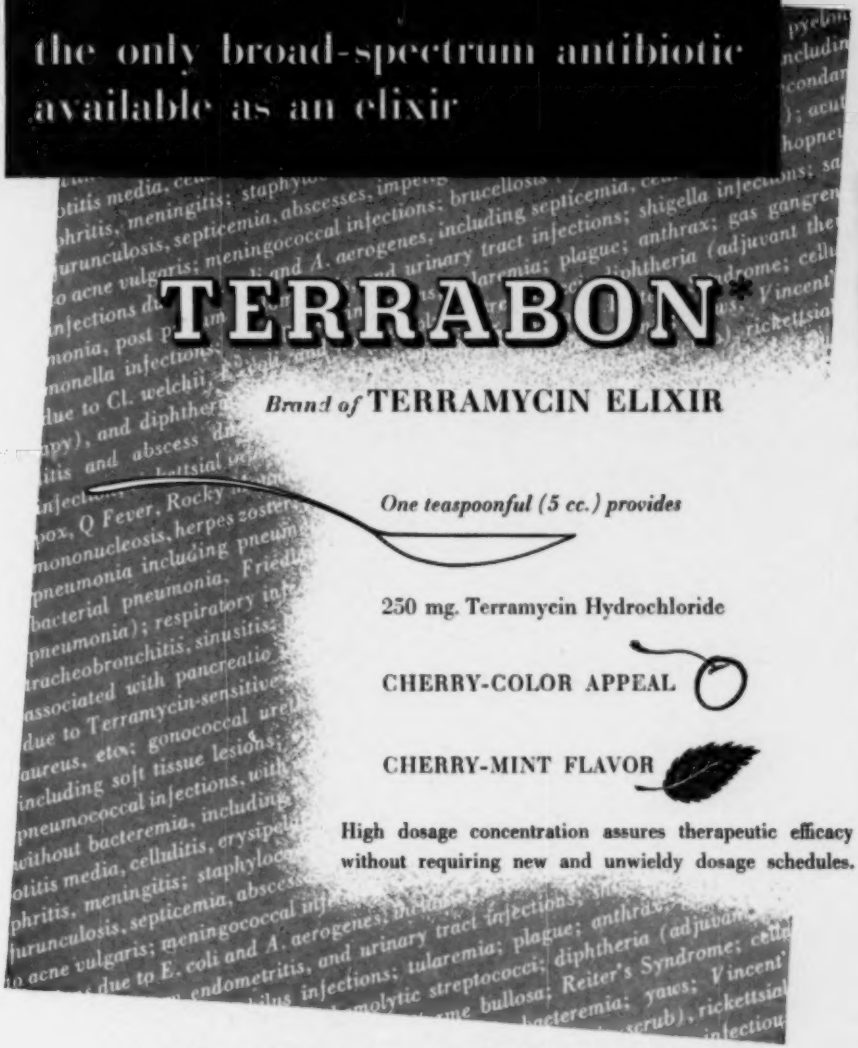
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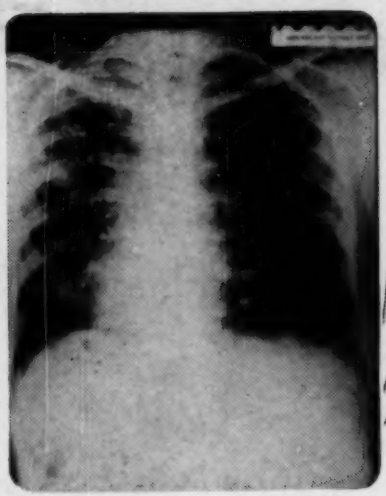

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